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(54) Title: INHIBITORS OF PROTEIN TYROSINE PHOSPHATASE

(57) Abstract

The present invention comprises small molecular weight, non–peptidic inhibitors of formula (I) of Protein Tyrosine Phosphatase 1 (PTP1) which are useful for the treatment and/or prevention of Non–Insulin Dependent Diabetes Mellitus (NIDDM).

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INHIBITORS OF PROTEIN TYROSINE PHOSPHATASE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of US application serial number 09/265,410 filed 10 March 1999, the entire contents of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention comprises small molecular weight, non-peptidic inhibitors of Protein Tyrosine Phosphatase 1 (PTP1) which are useful for the treatment and/or prevention of Non-Insulin Dependent Diabetes Mellitus (NIDDM).

BACKGROUND OF THE INVENTION

The mechanism of insulin action depends critically upon the phosphorylation of tyrosine residues in several proteins in the insulin signaling cascade. Enzymes that dephosphorylate these proteins, protein tyrosine phosphatases (PTPs), are important negative regulators of insulin action. Therefore, the use of specific PTP inhibitors may therapeutically enhance insulin action.

The insulin resistance that is central to noninsulin-dependent diabetes mellitus (NIDDM) appears to involve a defect in an early process in insulin signal transduction rather than a structural defect in the insulin receptor itself. (J.M. Olefsky, W.T. Garvey, R.R. Henry, D. Brillon, S. Matthai and G.R. Freidenberg, G.R. (1988).) Cellular mechanisms of insulin resistance in non-insulin-dependent (Type II) diabetes. (Am. J. Med. 85: Suppl. 5A, 86-105.) A drug that improved insulin sensitivity would have several advantages over traditional therapy of NIDDM using sulfonylureas, which do not alleviate insulin resistance but instead compensate by increasing insulin secretion.

The binding of insulin to the α-subunits of the insulin receptor permits the β-subunits to catalyze phosphorylation of target proteins on tyrosine residues. There are 22 tyrosine residues in each insulin receptor β-subunit itself and autophosphorylation of at least 6 of these tyrosines, in 3 distinct domains, is known to be involved in insulin action. (C.R. Kahn (1994) Insulin action, diabetogenes, and the cause of type II diabetes. Diabetes 43: 1066-1084.) Autophosphorylation of Tyr ^{960} in the juxtamembrane domain is important for receptor

internalization and for the interaction of the receptor with downstream signaling molecules such as insulin receptor substrate 1 (IRS-1).) (T.J. O'Neill, A. Craparo and T.A. Gustafson (1994) Characterization of an interaction between insulin receptor substrate 1 and the insulin receptor by using the two-hybrid system. Mol. Cell Biol. 14: 6433-6442.) Autophosphorylation of tyrosine residues 1146, 1150 and 1151 in the regulatory domain permits continued tyrosine kinase activity of β-subunits, even after insulin has dissociated from the α-subunits, and activates the kinase toward other protein substrates. (R. Herrera and O.M. Rosen (1986) Autophosphorylation of the insulin receptor *in vitro*: designation of phosphorylation sites and correlation with receptor kinase activation. J. Biol. Chem. 261: 11980-11985.) Deletion of autophosphorylation sites at Tyr^{1316} and Tyr^{1322} in the C-terminal domain attenuates the metabolic actions of insulin, but augments its mitogenic actions. (H. Maegawa, D. McClain, G. Freidenberg, J. Olefsky, M. Napier, T. Lipari, T. Dull, J. Lee, and A. Ullrich (1988) Properties of a human insulin receptor with a COOH-terminal truncation. II. Truncated receptors have normal kinase activity but are defective in signaling metabolic effects. J. Biol. Chem. 263: 8912-8917.) (Y. Takata, N.J.G. Webster, and J.M. Olefsky (1991) Mutation of the two carboxyl-terminal tyrosines results in an insulin receptor with normal metabolic signaling but enhanced mitogenic signaling properties. J. Biol. Chem. 266: 9135-9139.) Dephosphorylation of these autophosphorylated sites occurs rapidly *in vivo*, suggesting that a protein tyrosine phosphatase (PTPase) is involved in terminating insulin action. A compound that inhibited this PTPase, therefore, should potentiate insulin action. Indeed, vanadate potentiates insulin action, at least in part, by such a mechanism (Y. Schechter (1990). Insulin-mimetic effects of vanadate. Possible implications for future treatment of diabetes. Diabetes 39: 1-5.) The PTPase(s) that act on the insulin receptor, however, has not been identified definitively.

It has been estimated that the human genome encodes as many as 500 PTP enzymes (T. Hunter (1995) Protein kinases and phosphatases: The Yin and Yang of protein phosphorylation and signaling. Cell 80:225-236), but less than 100 have been identified and have been grouped into 4 sub-families (E.A. Fauman and M.A. Saper (1996) Structure and function of the protein tyrosine phosphatases. Trends Biochem. Sci. 21:413-417.) Members of the tyrosine-specific PTP sub-family are further divided into the receptor PTPases (such as CD45 and LAR) which typically have a large variable extracellular domain, a single transmembrane spanning region, and two intracellular phosphatase catalytic domains and the non-receptor PTPases. This latter group includes PTP that resemble PTP1. (D.A. Pot and J.E. Dixon (1992) A thousand and two protein tyrosine phosphatases. Biochim. Biophys. Acta 1136: 35-43.) There is data to support

the proposition that the insulin receptor PTPase may be PTP1-like. For instance, an insulin-dependent association of PTP1 with insulin receptors has been described. (D. Bandyopadhyay, A. Kursari, K.A. Kenner, F. Liu, J.Chernoff, T.A. Gustafson, J. Kusari (1997) Protein-tyrosine phosphatase 1B complexes with the insulin receptor *in vivo* and is tyrosine-phosphorylated in the presence of insulin. J.Biol.Chem. 272: 1639-1645; and L. Seely, et al. (1996) Protein tyrosine phosphatase 1B interacts with the activated insulin receptor. Diabetes 45:1379.) Furthermore, PTP1 dephosphorylates purified insulin receptors sequentially in the order observed *in vivo* (i.e., $Tyr^{1150} = Tyr^{1151} > Tyr^{1146}$), (C. Ramachandran, R. Aebersold, N. Tonks and D.A. Pot (1992) Sequential dephosphorylation of a multiply phosphorylated insulin receptor peptide by protein tyrosine phosphatases. Biochemistry 31: 4232-4238) and insulin acutely increases PTP1 mRNA in hepatoma cells. (N. Hashimoto and B.J. Goldstein (1992) Differential regulation of mRNAs encoding three protein-tyrosine phosphatases by insulin and activation of protein kinase C. Biochem. Biophys. Res. Commun. 188: 1305-1311.) Insulin resistance induced in Rat 1 fibroblasts by high glucose (27 mM) is preceded by an approximate doubling of cytosolic PTP1 activity that is blocked by the insulin-sensitizer, pioglitazone. (H. Maegawa, R. Ide, M. Hasegawa, S. Ugi, K. Egawa, M. Iwanishi, R. Kikkawa, Y. Shigeta, and A. Kashiwagi (1995) Thiazolidinedione derivatives ameliorate high glucose-induced insulin resistance via the normalization of protein tyrosine phosphatase activities. J. Biol. Chem. 270: 7724-7730.) Thus, a specific inhibitor of PTP1 could be used to potentiate insulin action. While there are no known small molecules that specifically inhibit PTP1, it was found that osmotic loading of hepatoma cells with neutralizing antibodies against PTP1b (the human homologue of rat PTP1) resulted in increased autophosphorylation of insulin receptors and phosphorylation of IRS-1 in response to insulin. (F. Ahmad, P.-M. Li, J. Meyerovitch, and B.J. Goldstein (1995) Osmotic loading of neutralizing antibodies demonstrates a role for PTPase 1B in negative regulation of the insulin signaling pathway. Diabetes 44: Suppl. 1 104A.) See also B.J. Goldstein (1993) Regulation of insulin receptor signaling by protein-tyrosine dephosphorylation. Receptor 3: 1-15.)

INFORMATION DISCLOSURE

International Publication No. WO 96/30332, "O-Malonyltyrosyl Compounds, O-Malonyltyrosyl Compound-Containing Peptides, and Uses thereof," published 3 October 1996, disclose non-phosphorus containing O-malonyltyrosyl compounds, derivatives thereof, uses of the O-malonyltyrosyl compounds in the synthesis of peptides, and O-malonyltyrosyl compound-

containing peptides. The O-malonyltyrosyl compounds and O-malonyltyrosyl compound-containing peptides are disclosed as being useful as inhibitors of protein-tyrosine phosphatase; however, no specific non-peptidic compounds or data is disclosed.

International Publication No. WO 96/23813, "Peptides and Compounds that Bind to SH2 Domains," published 8 August 1996, discloses tyrosine-containing peptides and compounds which bind to the SH2 domain or domains of various proteins, as well as methods for identifying such peptides and compounds. These peptides and compounds have application as agonists and antagonists of SH2 domain containing proteins, and as diagnostic or therapeutic agents for the diagnosis or treatment of disease conditions.

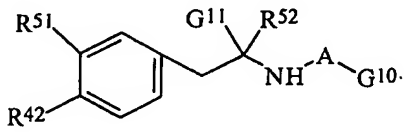
International Publication No. WO 96/40113, "Phosphatase Inhibitors," published 19 December 1996, discloses heterocyclic nitrogen containing compounds, such as nitropyridine or nitrothiazole, capable of inhibiting protein tyrosine phosphatase activity. Such molecules are disclosed as being useful to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity and to treat various disease states including diabetes mellitus.

International Publication No. WO 96/40109, "Methods of Inhibiting Phosphatase Activity and Treatment of Disorders Associated Therewith Using Napthopyrones and Derivatives Thereof," published 19 December 1996, discloses the use of naphthopyrone compounds to inhibit protein tyrosine phosphatase activity. Such compounds are disclosed as being useful to modulate or regulate signal transduction by inhibiting protein tyrosine phosphatase activity and to treat various disease states including diabetes mellitus.

The compounds of the present invention have surprising activity in that they are small molecular weight and non-peptidic compounds.

SUMMARY OF THE INVENTION

One aspect of the invention provides a compound of formula I:



I

wherein A is –C(O)- or $-SO_2$-;

wherein G^{10} is $-R^{43}$;

wherein G^{11} is

a) $CONR^{99}R^{44}$,

b) H,

c) CH_2OH, or

d) $CH{=}CHR^{44}$;

wherein R^{99} is H or C_1-C_6 alkyl;

wherein R^{42} is

a) $-OSO_3H$,

b) $-OCH(CO_2R^{46})_2$,

c) $-OCH_2(CO_2R^{46})$,

d) $-OCH(CO_2R^{46})CH_2CO_2R^{46}$,

e) $-OC(CO_2R^{46}){=}CHCO_2R^{46}$,

f) $-CH_2CH(CO_2R^{46})_2$,

g) $-CH{=}C(CO_2R^{46})_2$,

h) $-OCH_2CONHOH$,

i) $-N(CH_2CO_2R^{46})_2$, or

j) $-OCHF(CO_2R^{46})$;

wherein R^{43} is

a) -C_1-C_{10} alkoxy,

b) -C_0-C_6 alkyl-$(G^{12})_n$, wherein alkyl is optionally substituted with one to three -O-C_1-C_4 alkyl, halo, or trifluoromethyl, and optionally interrupted with one to three -O-, -S-, or -N-, with the proviso that when G^{12} is phenyl, the phenyl group must be substituted by one (1) to four (4) R^{50} groups, provided that $-COOR^{46}$ is not a substituent,

c) -C_2-C_{10} alkenyl-$(G^{12})_n$,

d) -C_1-C_{10} alkyl-O-$(G^{12})_n$,

e) -C_1-C_6 alkyl-C_3-C_{10} cycloalkyl optionally substituted with one to three R^{50}, or

f) -C_0-C_{10} alkylcarbonyl-$(G^{12})_n$ wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-;

wherein R^{44} is

a) -C_1-C_{12} alkyl, optionally substituted with one to three -O-C_1-C_4 alkyl, -S-C_1-C_4 alkyl, -O-G^{12}, -S-G^{12}, or -OH, and optionally interrupted with one to three -O-, -S-, or -N-,

b) -C_1-C_4 alkyl-C_3-C_6 cycloalkyl,

c) -C_2-C_{12} alkenyl,

d) -C_3-C_{12} alkynyl,

e) -C_0 –C_{10} alkyl$(G^{12})_n$ wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-,

f) -$CH(CONH_2)C_1$-C_{12} alkyl,

g) –C_0-C_6 alkyl-$NR^{53}R^{54}$, wherein alkyl is substituted with zero to three OH,

h) –NR^{54}-CO-R^{56}, or

i) –O-C_1-C_{10} alkyl$(G^{12})_n$, wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-;

wherein R^{46} is

a) -H,

b) -C_1-C_{10} alkyl, or

c) -C_1-C_5 alkyl-phenyl;

wherein R^{47} is

a) -C_1-C_{10} alkyl,

b) -C_0-C_6 alkyl-G^{12},

c) -C_1-C_6 alkyl-$CONH_2$,

d) -C_1-C_6 alkyl $NHCO_2R^{46}$,

e) -C_1-C_6 alkyl-OR^{46},

f) -C_1-C_6 alkyl-$NHSO_2Me$,

g) -C_1-C_6 alkyl-O-G^{12},

h) -C_1-C_6 alkyl-S-G^{12}, or

i) -C_1-C_6 alkyl-CO_2R^{46};

wherein R^{48} is

a) -H,

b) -C_1-C_6 alkyl-G^{12},

c) -C_1-C_6 alkyl-CO_2R^{46},

d) -C_1-C_6 alkyl $CONH_2$,

e) -C_1-C_6 alkyl $NHCO_2R^{46}$,

f) -C_1-C_{10} alkyl,

g) -C_1-C_{10} cycloalkyl,

h) -C_1-C_6 alkyl-SR^{46}, or

i) -C_1-C_6 alkyl-$S(=O)R^{46}$;

wherein G^{12} is

a) phenyl substituted by zero (0) to four (4) R^{50},

b) naphthyl substituted by zero (0) to three (3) R^{50}, or

c) het_1 substituted by zero (0) to three (3) R^{50};

wherein het_1 is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and optionally, the nitrogen and sulfur heteroatoms may be in oxidized form if chemically feasible;

wherein R^{50} may be any of the following:

a) C_1-C_8 alkyl substituted by zero (0) to three (3) halo,

b) C_2-C_8 alkenyl,

c) OH,

d) O-C_1-C_5 alkyl,

e) O-C_0-C_5 alkyl-phenyl,

f) -$(CH_2)_n$-O-C_1-C_5 alkyl substituted by zero (0) to three (3) hydroxy,

g) -$(CH_2)_n$-O-C_2-C_7 alkenyl substituted by zero (0) to three (3) hydroxy,

h) halo,

i) NH_2,

j) amino-C_1-C_5 alkyl,

k) mono-or di-C_1-C_5 alkylamino,

l) -C(O)-C_1-C_5 alkyl,

m) -CHO,

n) -C(O)-C_0-C_5 alkyl-phenyl,

o) -$COOR^{46}$,

p) -$CON(R^{46})_2$,

q) $-C_3$-C_7 cycloalkyl,

r) $-NO_2$,

s) -CN,

t) $-SO_3H$,

u) $-SO_2N(R^{46})_2$,

v) $-O[(CH_2)_2-O]_n-CH_3$,

w) $-[CH_2-O]_n-C_1$-C_3 alkyl,

x) $-NR^{46}(CO)-NR^{46}$,

y) $-CF_3$,

z) $-NR^{46}(CO)C_1$-C_5 alkyl,

a1) $-N(R^{46})-SO_2-R^{46}$,

b1) $-O-C(O)-R^{46}$,

c1) $-S(O)-R^{46}$,

d1) $-SR^{46}$,

e1) $-SO_2-R^{46}$,

f1) phenyl, or

g1) oxo;

wherein R^{51} is

a) -H,

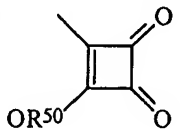
b) $-CO_2R^{46}$,

c) -CONHOH,

d) het_2 substituted by zero to three R^{50}, where in het_2 is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

e) F,

f) $OCH_2CO_2R^{46}$, or

g) 

wherein R^{52} is

a) H, or

b) methyl;

wherein R^{53} and R^{54} are

a) H,

b) C_1-C_6 alkyl, or

c) C_0-C_6 alkyl-phenyl;

wherein R^{55} is

a) H, or

b) C_1-C_4 alkyl;

wherein R^{56} is

a) C_0-C_6 alkyl-phenyl, wherein alkyl is optionally substituted with one OH and phenyl is substituted with one to three OH or phenyl, or

b) C_0-C_6 alkyl-NR^{55}-CO-phenyl, wherein alkyl is optionally substituted with one OH and phenyl is substituted with zero to three OH or phenyl;

wherein X is -CO- or -SO_2- or -CO_2-;

wherein n is zero, one, two or three;

or a pharmaceutically acceptable salt thereof;

provided that when R^{51} is H, R^{42} is other than -$OCH_2(CO_2R^{46})$; and that when (i) A is –SO_2-; and/or (ii) R^{44} is –C_0-C_6 alkyl-$NR^{53}R^{54}$, wherein alkyl is substituted with zero to three OH; and/or (iii) R^{44} is -NR^{54}-CO-R^{56}; and/or (iv) R^{44} is –O-C_1-C_{10} alkyl $(G^{12})_n$, wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-; and/or (v) R^{51} is het_2 other than 5-tetrazolyl; and/or (vi) R^{99} is C_1-C_6 alkyl; then

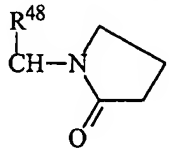
(1) R^{43} may also be

g) -C_1-C_{10} alkyl optionally substituted with (i) one or two -CO_2R^{46} bonded to the same or different carbon atoms or (ii) one –CO-NH_2,

h) –C_0-C_6 alkyl-C_3-C_8 cycloalkyl optionally substituted with one –CO_2R^{46},

i) –C_0-C_6 alkyl-phenyl optionally substituted with (i) one or two –CO_2R^{46} bonded to the same or different carbon atoms or (ii) –$CH_2CH(CO_2R^{46})_2$,

j) –$CH(R^{48})NHXR^{47}$, or

k) 

;

and

(2) G^{10} may also be

b) $-NR^{49}R^{45}$;

wherein R^{45} is

a) -H,

b) $-C_1$-C_{18} alkyl or alkenyl, or

c) $-C_0-C_6$ -alkyl-G^{12}; and

wherein R^{49} is

a) C_0-C_6 alkyl-G^{12},

b) $CH(R^{48})CO_2R^{46}$,

c) $CH(R^{48})CH_2CO_2R^{46}$, or

d) $CH(R^{48})CONHCH_2CO_2R^{46}$.

Another aspect of this invention provides a pharmaceutical composition, comprising the compounds of formula I and a pharmaceutically acceptable carrier.

Another aspect of this invention provides a method for treating a patient by administering an effective amount of a compound of formula I.

Another aspect of this invention provides a method of inhibiting protein tyrosine phosphatases, comprising contacting a cell with the compounds of formula I.

Another aspect of this invention provides the compounds of formula I above excluding the compounds disclosed in U.S. Serial No. 09/138,642 and PCT/US98/17327, which are hereby incorporated by reference.

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

The carbon atoms content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_1-C_3 alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl, straight and branched forms thereof.

Also, the carbon atom content of various hydrocarbon-containing moieties of the present invention may be indicated by a subscripted integer representing the number of carbon and hydrogen atoms in the moiety, e.g., "C_nH_{2n}" indicates a moiety of the integer "n" carbon atoms, inclusive, and the integer "2n" hydrogen atoms, inclusive. Thus, for example, "C_nH_{2n}" wherein

n is one to three carbon atoms, inclusive, and two to six hydrogen atoms, inclusive, or methyl, ethyl, propyl and isopropyl, and all isomeric, straight and branched forms thereof.

Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms thereof and straight and branched forms thereof.

Examples of alkenyl of one to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, all isomeric forms thereof, and straight and branched forms thereof.

By "halo" is meant the typical halogen atoms, such as fluorine, chlorine, bromine, and iodine.

The present invention encompasses all possible combinations of configurations at each of the possible chiral centers. The preferred configuration for the chiral center depicted in formula I is (S).

The compounds of formula I of the present invention are prepared as described in the Charts, Preparations and Examples below, or are prepared by methods analogous thereto, which are readily known and available to one of ordinary skill in the art of organic synthesis.

The present invention provides for compounds of formula I or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability, patient acceptance and bioavailability. Examples of salts of the compounds of formula I include lithium, sodium and potassium.

Where R^{46} is other than H, the compounds would not be expected to have intrinsic activity, but would be expected to possess activity *in vivo* following hydrolysis by non-specific esterases to the corresponding carboxylic acids.

The compounds of the present invention are useful for treating patients, such as human patients, with noninsulin-dependent diabetes mellitus (NIDDM) and conditions resulting from NIDDM, such as obesity. For this indication, these compounds may be administered by oral, intranasal, transdermal, subcutaneous and parenteral (including intramuscular and intravenous) routes in doses of 0.1 mg to 1000 mg/kg of body weight per day.

Those skilled in the art would know how to formulate the compounds of this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

When the compounds in this invention are administered orally, an effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions, such as compressed tablets, are prepared by mixing the compounds of this invention with conventional pharmaceutical carriers such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum.

Syrups are prepared by dissolving the compounds of this invention in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds of this invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 0.1 mg to 100 mg per kg of body weight per day. Parenteral solutions are prepared by dissolving the compounds of this invention in aqueous vehicle and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skilled in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

The utility of representative compounds of the present invention has been demonstrated in the biological assays described below:

PTP1 Assays: A construct, which consisted of a C-terminal truncation of rat PTP1 (amino acid residues 1-322) (cloned from a rat brain library) with an N-terminal glutathione S-transferase (GST) tag and an adjacent thrombin cleavage site, was inserted into vector plasmid pGEX-2T and transformed into E.coli strain TG-1 under the control of a lac promoter (K. L. Guan and J. E. Dixon (1991) Eukaryotic proteins expressed in Escherichia coli: an improved thrombin cleavage and purification procedure of fusion proteins with glutathione S-transferase.

Analyt. Biochem. 192: 262-267). The GST-fusion protein was purified on a glutathione agarose affinity column, the GST tag was cleaved with thrombin, and the active enzyme was recovered for use in an assay to identify PTP inhibitors.

The equivalent construct of human PTP1B (amino acid residues 1-321) (cloned from a human placental library), without the GST tag and thrombin cleavage site, was inserted into a pMB replicon and transformed into E. coli BL21(DE3), a strain containing a chromosomal copy of the gene for T7 RNA polymerase under control of a lacUV5 promoter. Expression of PTP1B was induced with isopropyl thiogalactose and the soluble protein was purified by ion exchange, hydrophobic interaction and gel exclusion chromatography for use in the assay to identify PTP inhibitors.

PTP1 activity is measured using either p-nitrophenol phosphate (pNPP) or a triphosphopeptide (that matches residues 1142 through 1153 of the β-subunit and the insulin receptor) as substrate in a 96-well microtiter plate format. An assay pH of 7.2 is used for standard assays (measured A_{405}=9800 at pH 7.2).

Human PTP1B, which is highly homologous to rat PTP1, was assayed exactly as described above for PTP1. The PTP1 inhibitors described here also inhibit PTP1B with similar or identical potencies.

Standard assays are conducted at room temperature in a total volume of 0.2 ml that contains Hepes buffer (50 mM, pH 7.2), NaCl (50 mM), EDTA (1 mM), DTT (1 mM), bovine serum albumin (1 mg/ml), pNPP (1 mM) and PTP1 (35 ng/ml). Compounds (2 µl of 10 mM solutions) are pipetted into wells of microtiter plates followed by 198 µl of premixed reaction mix (with PTP1 and pNPP added immediately before use). The rate of change in A_{405} is recorded for 60 min. Two wells on each plate contain DMSO controls and two wells contain sodium orthovanadate (1 mM) which inhibits PTP1-catalyzed hydrolysis of pNPP completely. Data are expressed as percent inhibition relative to the average of the DMSO controls measured on the same microtiter plate.

When triphosphopeptide$^{1142\text{-}1153}$ is used as substrate, the rate of release of inorganic phosphate is measured using a Malachite Green/phosphomolybdate reaction (A.A. Baykov, O.A. Evtushenko, and S.M. Avaeva (1988) A Malachite Green procedure for orthophosphate determination and its use in alkaline phosphatase-based enzyme immunoassay. Anal. Biochem. 171: 266-270.) in a microtiter plate format. Standard assays are conducted at room temperature in a total volume of 50 µl that contains Hepes buffer (50 mM, pH 7.2), NaCl (50 mM), EDTA

(1mM), DTT (1mM), bovine serum albumin (1mg/ml), triphosphopeptide$^{1142-1153}$ (200 μM) and PTP1 (87 ng/ml). Reactions are terminated with the addition of 0.15 ml of Malachite Green/ ammonium molybdate reagent [10ml Malachite Green (0.44 g in 6N H_2SO_4), 2.5 ml ammonium molybdate (7.5% w/v), 0.2 ml Tween 20 (11% w/v)] that is diluted with 8 parts of water immediately before use, and after 1 h absorbance at 650 nm is measured. The phosphate assay is calibrated using either KH_2PO_4 or pNPP (after ashing with $Mg(NO_3)_2$) which gives essentially identical standard curves. The phosphate assay is useful in the range of 1 to 10 nmol P_i.

The % inhibition of pNPP-hydrolysis by compounds of the present invention are listed in Table 1 below.

The invention is further directed to the following compounds:

2-(carboxymethoxy)-5-[(2S)-3-oxo-3-(pentylamino)-2-({(2S)-2-[(phenoxycarbonyl)amino]-3-phenylpropanoyl}amino)propyl]benzoic acid;

5-((2R)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[3-(2-oxo-1-pyrrolidinyl)propyl]amino}propyl)-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-pyridinylmethyl)amino]propyl)-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-isopropoxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-hydroxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-[(2R)-2-{[2-(2-methoxyphenyl)acetyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid;

Methyl-2-[4-{(2S)-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetate;

2-[4-{(2S)-2-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetic acid;

2-[4-{(2S)-3-furoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5- yl)phenoxy]acetic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylpropoxy)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(2-hydroxyethyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylpropyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-hydroxypropy]-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid;

5-{(2S)-2-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-{(2S)-2-[(4-chlorobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid;

2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid;

2-(carboxymethoxy)-5-{(2S)-2-(3-furoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid;

5-((2S)-2-(benzoylamino)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-((2S)-2-[(4-chlorobenzoyl)amino]-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-(3-furoylamino)-3-oxopropyl]benzoic acid;

2-(carboxymethoxy)-5-((2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(2,4-diflurophenyl)sulfonyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-({[(E)-2-phenylethenyl]sulfonyl}amino)propyl]benzoic acid; and

2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(3-phenoxypropyl)amino]-2-[(phenylsulfonyl)amino]propyl}benzoic acid.

DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1: (Chart A, Formula A-7) 2-[4-{(2S)-2-(benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]-propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetic acid

PREPARATION OF A-2: To a stirring solution of A-1 (0.25 g, 0.61 mmol) in CH_2Cl_2 (4 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.13 g, 0.67 mmol) and 4-phenylbutylamine (107 µL, 0.67 mmol) at 0 °C. The mixture was strirred at ambient temperature over night, and then extracted with 1 M aqueous HCl (2 x 2 mL) and brine (4 mL). The organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography (SiO_2, EtOAc/iso-hexane 1:1) which furnished 0.28 g (85%) of A-2 as a colorless oil. ^{1}H NMR 500 Mz ($CDCl_3$) δ 1.41 (s, 9H), 1.43 (m, 2H), 1.54 (m, 2H), 2.59 (dd, 2H), 2.92 (m, 2H), 3.18 (m, 2H), 4.18 (m, 1H), 5.07 (br s, 1H), 5.81 (br s, 1H), 6.85 (d, 1H, J = 8,1 Hz), 7.05 (dd, 1H, J = 8.1, 1.6 Hz), 7.13-7.49 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.4, 29.0, 35.4, 37.3, 39.4, 40.5, 56.1, 65.3, 80.4, 85. 4, 115.1, 125.8, 128.3, 128.4, 131.0, 138.9, 141.9, 154.2, 155.4, 170.9. IR 3312, 3010, 2932, 1660,1500, 1367 cm^{-1}. MS (ESI) 537 (M-H). HRMS (EI) calcd for $C_{24}H_{31}IN_2O_4$ 538.1329, found 538.1315.

PREPARATION OF A-3: To a solution of A-2 (7.0 g, 13 mmol) in THF (50 mL) was added zinc cyanide (1.83 g, 15.6 mmol), $Pd(PPh_3)_4$ (0.75g, 0.65 mmol) and copper(I)iodide (0.25 g, 1.30 mmol). The mixture was refluxed (75 °C) over night, under nitrogen atmosphere. The reaction mixture was cooled to ambient temperature, diluted with EtOAc and filtered through a pad of celite. The filtrate was concentrated and purified by flash chromatography (SiO_2, gradient: EtOAc/iso-hexan 1:3 to EtOAc/iso-hexane 1:1) which furnished 1.40 g of a mixture of starting material and product, and 2.51 g of A-3 (44%) as a white solid. ^{1}H NMR 400 MHz (MeOH) δ 1.37 (s, 9H), 1.46 (m, 2H), 1.57 (m, 2H), 2.60 (m, 2H), 2.74 (dd, 1H, J = 8.8, 13.8), 2.96 (dd, 1H, J = 6.3, 13.8), 3.12 and 3.18 (m, 2H), 4.16 (m, 1H), 6.87 (d, 1H, J = 8.5), 7.11-7.36 (m, 7H); ^{13}C NMR (MeOH) δ 28.6, 29.9, 30.94, 36.4, 38.2, 40.2, 40.8, 57.3, 80.7, 100.5, 117.1, 117.9, 126.7, 129.3, 129.4, 130.2, 134.9, 136.8, 143.5, 157.5, 160.4, 173.7. MS 436 (M-H).

PREPARATION OF A-4: To a solution of A-3 (2.51 g, 5.74 mmol) in acetone (30 mL) was added methyl bromoacetate (1.09 mL, 11.47 mmol) and grounded K_2CO_3 (1.59 g, 11.47). The mixture was stirred at 50 °C over night and then cooled to ambient temperature. Water (20 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL), the organic layer was dried (Na_2SO_4) and concentrated. The crude material was purified by flash chromatography

(SiO2, EtOAc/iso-hexane 1:1) which furnished 2.21 g (76%) of A-4 as a white solid. Mp 94-96 °C. ^{1}H NMR 500 MHz ($CDCl_3$) δ 1.40 (s, 9H), 1.46 (m, 2H), 1.58 (m, 2H), 2.61 (m, 2H), 2.95 (dd, 1H, J = 6.9, 14.1), 3.05 (dd, 1H, J = 6.9, 14.1), 3.22 (m, 2H), 3.79 (s, 3H), 4.21 (m, 1H), 4.71 (s, 2H), 5.01 (br s, 1H), 5.96 (br m, 1H), 6.73 (d, 1H, J = 8.5), 7.14-7.28 (m, 5H), 7.35 (dd, 1H, J = 8.5, 2.2), 7.42 (d, 1H, J = 2.2); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.4, 29.0, 29.8, 35.3, 35.5, 37.1, 39.4, 40.5, 52.4, 55.6, 65.7, 80.5, 102.7, 112.5, 115.8, 125.8, 128.4, 130.9, 134.5, 135.2, 142.1, 158.4, 168.2, 170.4. IR 3338, 2932, 2863, 2224 (CN signal), 1754, 1681, 1646. MS (ESI) 508 (M-H). Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.25. Found: C, 66.9; H, 7.0; N, 8.2.

PREPARATION OF A-5: Trifluoroacetic acid (2.1 mL) was carefully added to a stirring solution of A-4 (0.93 g, 1.82 mmol) in CH_2Cl_2 (17 mL) at 0 °C. The mixture was stirred for 3h allowing the solution to warm to ambient temperature. The volatiles were removed by evaporation in vacuo, and the residue was partitioned between EtOAc (15 mL) and saturated aqueous $NaHCO_3$ (2x10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 0.90 g (>100%) of the crude amine as a yellowish oil. The amine was dissolved in CH_2Cl_2 (15 mL) and cooled with ice. Benzoic acid (0.22 g, 1.82 mmol), 1-hydroxybenzotriazole (0.25 g, 1.82 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.35 g, 1.82 mmol) was added to the solution, which was then stirred at room temperature over night. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc) which gave 0.65 g (69%) of A-5 as a white solid. Mp = 125-128 °C. ^{1}H NMR 500 MHz($CDCl_3$) δ 1.43 (m, 2H), 1.54 (m, 2H), 2.55 (t, 2H, J = 7.2, 15.1 Hz), 3.13 (m, 3H), 3.21 (m, 1H), 3.77 (s, 3H), 4.68 (s, 2H), 4.86 (m, 1H), 6.48 (br t, 1H), 6.71 (d, 1H, J = 8.8 Hz), 7.10 (d, 3H), 7.15 (m, 1H), 7.24 (m, 2H), 7.39 (m, 3H), 7.49 (m, 1H), 7.71 (m, 2H); ^{13}C NMR (CDCl3) δ 28.4, 28.9, 35.3, 37.4, 39.4, 52.4, 54.7, 65.6, 102.6, 112.5, 115.8, 125.8, 127.0, 128.3, 128.7, 130.8, 132.0, 133.4, 134.7, 135.2, 141.9, 158.5, 167.4, 168.1, 170.4. IR 3278, 2932, 2855, 2224 (CN signal), 1750, 1630, 1500. MS (ESI) 512 (M-H). Anal. Calcd for $C_{30}H_{31}N_3O_5$: C, 70.16; H, 6.08; N, 8.18. Found: C, 70.3; H, 6.1; N, 8.2.

PREPARATION OF A-6: To a suspension of A-5 (0.21 g, 0.42 mmol) in toluene (4 mL) in a Heck vial was added trimethylsilyl azide (165 μL, 1.25 mmol) and dibutyltin oxide (10.3 mg, 0.042 mmol). The flask was flushed with nitrogen, tightly sealed, and stirred at 95 °C over night. Some more trimethylsilyl azide (3 eq.) and dibutyltin oxide (0.1 eq.) was added two times

and the mixture was continuously stirred at 95 °C. After 48 h the reaction mixture was cooled to ambient temperature, and the volatiles were evaporated in vacuo. The residue was partitioned between EtOAc (5 mL) and 1 M aqueous HCl (3 mL). The organic layer was washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The material was purified by flash chromatography (SiO_2, gradient system: EtOAc/ iso-hexane 1:1 to 3:1) which furnished 49 mg (21%) of A-6 as a white solid. Mp = 183-186 °C. ^{1}H NMR 500 MHz (MeOH) δ 1.46 (m, 2H), 1.53 (m, 2H), 2.53 (t, 2H, J = 7.2, 14.8), 3.07-3.16 (m, 2H), 3.23 (m, 2H), 3.79 (s, 3H), 4.80 (m, 1H, hidden behind solvent peak), 4.93 (s, 2H), 7.06 (d, 1H), 7.11 (m, 3H), 7.19 (m, 2H), 7.40 (m, 2H), 7.45-7.51 (m, 2H), 7.75 (m, 2H), 8.18 (d, 1H); ^{13}C NMR (MeOH) δ 29.7, 29.9, 36.3, 38.2, 40.2, 53.0, 56.7, 66.8, 114.3, 115.5, 126.7, 128.5, 129.3, 129.4, 129.5, 131.7, 132.8, 135.0, 135.2, 143.5, 153.3, 155.6, 170.1, 171.5, 173.2. IR 3286, 2924, 2855, 1742, 1634, 1500. MS (ESI) 555 (M-H). Anal. Calcd for $C_{30}H_{32}N_6O_5$: C, 64.74; H, 5.79; N, 15.10. Found: C, 64.8; H, 5.8; N, 15.1.

PREPARATION OF A-7: To a solution of A-6 (33 mg, 0.060 mmol) in THF (0.8 mL) was added 2.5 M aqueous LiOH (72 μL, 0.18 mmol). The mixture was stirred at room temperature for 4 h, and then quenched with 1 M aqueous HCl. The mixture was diluted with EtOAc (3 mL). Some precipitate was formed which was filtered off by a glass funnel. The filtrate was washed with brine (3 mL) and the organic layer was dried (Na_2SO_4), and concentrated in vacuo, which furnished a white solid. This material was combined with the precipitate, which totally gave 28 mg (84%) of A-7 as a white solid. Mp = 223-225 °C. ^{1}H NMR 500 MHz (MeOH) δ 1.44 (m, 2H), 1.53 (m, 2H), 2.53 (t, 2H, J = 7.5, 15.3 Hz), 3.08-3.17 (m, 2H), 3.21-3.26 (m, 2H), 4.79 (m, 1H, partly hidden behind solvent peak), 4.89 (s, 2H), 7.09 (m, 4H), 7.19 (m, 2H), 7.40 (m, 2H), 7.49 (m, 2H), 7.76 (m, 2H), 8.20 (d, 1H); ^{13}C NMR (MeOH) δ 29.7, 29.9, 36.3, 38.2, 40.2, 56.7, 67.0, 114.1, 114.8, 126.7, 128.5, 129.3, 129.5, 131.5, 132.8, 133.0, 135.2, 135.3, 143.5, 153.1, 155.8, 170.1, 173.1, 173.2. IR 3286, 3062, 2924, 1655, 1630, 1539, 1496, 1242. MS (ESI) 541 (M-H). Anal. Calcd for $C_{29}H_{30}N_6O_5 \cdot ¼\ H_2O$: C, 62.13; H, 5.75; N, 14.99. Found: C, 62.4; H, 5.4; N, 14.8.

EXAMPLE 2: (Chart B, Formula B-4) 2-[4-{(2S)-2-(3-furoylamino)-3-oxo-3-[(4-phenylbutyl)amino]-propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetic acid

PREPARATION OF B-2: Trifluoroacetic acid (1.9 mL) was carefully added to a stirring solution of A-4 (0.85 g, 1.66 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 3h allowing the solution to warm to ambient temperature. The volatiles were removed by

evaporation in vacuo, and the residue was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (2x5 mL). The organic layer was dried (Na_2SO_4) and concentrated to give 0.71 g (>100%) of the crude amine as a yellowish oil. The amine was dissolved in CH_2Cl_2 (8 mL) and cooled with ice. 3-Furoic acid (0.21 g, 1.83 mmol), 1-hydroxybenzotriazole (0.25 g, 1.83 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.35 g, 1.82 mmol) was added to the solution, which was then stirred at room temperature over night. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (SiO_2, EtOAc/iso-hexane 1:1 to 3:1), which gave 0.51 g (62%) of B-2 as a colorless oil. ^1H NMR 500 MHz ($CDCl_3$) δ 1.44 (m, 2H), 1.56 (m, 2H), 2.57 (t, 2H, J = 7.3, 15.1 Hz), 3.06 (t, 2H, partly hidden behind multiplet), 3.13 (m, 1H), 3.24 (m, 1H), 3.76 (s, 3H), 4.68 (s, 2H), 4.82 (m, 1H), 6.61 (d, 1H), 6.72 (m, 1H), 7.11-7.17 (m, 3H), 7.24 (t, 2H), 7.34-7.38 (m, 2H), 7.48 (d, 1H), 7.91 (d, 1H); 13C NMR ($CDCl_3$) δ 28.5, 28.9, 35.3, 37.1, 39.5, 52.4, 54.6, 65.6, 102.6, 108.3, 112.5, 115.8, 121.8, 125.8, 128.3, 130.9, 134.7, 135.2, 141.9, 143.8, 145.3, 158.4, 162.8, 168.1, 171.0. MS (ESI) 502 (M-H). Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 66.79; H, 5.80; N, 8.34. Found: C, 66.6; H, 5.9; N, 8.3.

PREPARATION OF B-3: To a suspension of B-2 (0.44 g, 0.88 mmol) in toluene (5 mL) in a Heck vial was added trimethylsilyl azide (349 μL, 2.64 mmol) and dibutyltin oxide (22 mg, 0.088 mmol). The flask was flushed with nitrogen, tightly sealed, and stirred at 95 °C over night. Some more trimethylsilyl azide (3 eq.) and dibutyltin oxide (0.1 eq.) was added two times and the mixture was continuously stirred at 95 °C. After 48 h the reaction mixture was cooled to ambient temperature, and the volatiles were evaporated in vacuo. The residue was partitioned between EtOAc (5 mL) and 1 M aqueous HCl (3 mL). The organic layer was washed with brine (3 mL), dried (Na_2SO_4), and concentrated. The material was purified by flash chromatography (SiO_2, gradient system: EtOAc/ iso-hexane 1:1 to 3:1) which furnished 52 mg (11%) of B-3 as a white solid. Mp = 152-154 °C. ^1H NMR 500 MHz (MeOH) δ 1.44 (m, 2H), 1.53 (m, 2H), 2.53 (t, 2H), 3.05-3.25 (m, 4H), 3.81 (s, 3H), 4.78 (m, 1H), 4.91 (s, 2H), 6.79 (s, 1H), 7.05-7.23 (m, 6H), 7.48 (m, 2H), 8.07 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (MeOH) δ 29.7, 29.8, 36.3, 38.1, 40.2, 53.0, 56.2, 66.7, 109.7, 113.9, 114.4, 123.2, 126.7, 129.2, 129.3, 131.5, 132.9, 135.1, 143.4, 145.1, 146.8, 152.9, 155.5, 164.9, 171.4, 173.1. IR 3140, 2933, 2860, 2367, 1736, 1653, 1617, 1493. MS (ESI) 545 (M-H). Anal. Calcd for $C_{28}H_{30}N_6O_6$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.4; H, 5.8; N, 15.4.

PREPARATION OF B-4: To a solution of B-3 (40 mg, 0.073 mmol) in THF (0.8 mL) was added 2.5 M aqueous LiOH (88 μL, 0.22 mmol). The mixture was stirred at room temperature for 4 h, and then washed with EtOAc (2 mL). The aqueous layer was acidified with 1 M aqueous HCl and extracted with EtOAc (2 x 3 mL). Some precipitate was formed which was filtered off by a glass funnel. The filtrate was washed with brine (3 mL) and the organic layer was dried (Na_2SO_4), and concentrated in vacuo, which furnished a white solid. This material was combined with the precipitate, which totally gave 14 mg (37%) of B-4 as a white solid. Mp = 230-233 °C. ^{1}H NMR 500 MHz (MeOH) δ 1.42 (m, 2H), 1.50 (m, 2H), 2.51 (t, 2H, J = 7.5, 15.1 Hz), 3.07-3.13 (m, 2H), 3.19-3.23 (m, 2H), 4.75 (m, 1H), 4.91 (s, 2H), 6.78 (d, 1H, J = 2.5), 7.07-7.20 (m, 2H), 7.47 (dd, 1H), 7.53 (t, 1H), 8.06 (s, 1H), 8.17 (d, 1H, J = 2.5); ^{13}C NMR δ 29.7, 29.8, 36.3, 38.1, 40.2, 56.2, 66.9, 109.7, 111.0, 114.0, 114.7, 123.2, 126.7, 129.3, 129.4, 131.4, 132.9, 135.2, 143.5, 145.2, 146.8, 155.7, 173.0, 173.1. IR 3300, 2940, 2867, 1637, 1543, 1497, 1173. MS (ESI) 531 (M-H). Anal. Calcd for $C_{27}H_{28}N_6O_6 \cdot ¼ H_2O$: C, 60.38; H, 5.25; N, 15.65. Found: C, 60.2; H, 5.2; N, 15.4.

EXAMPLE 3: (Chart C, Formula C-3) 5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-hydroxypropyl]-2-(carboxymethoxy)benzoic acid

PREPARATION OF C-2: Methyl 5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-hydroxypropyl]-2-(2-methoxy-2-oxoethoxy)benzoate: To a solution of II-1 (1.24 g, 2.24 mmol) in dry THF (10 mL) is added 1,1'-carbonyldiimidazole (CDI, 0.54 g, 3.35 mmol). The solution is stirred at room temperature over night under nitrogen atmosphere. The reaction mixture is cooled with ice and a solution of $NaBH_4$ (0.21 g, 5.59 mmol) in H_2O (5 mL) is slowly added. After addition is complete, the mixture is stirred at room temperature for 10 min. The mixture is quenched with 10% aqueous HCl, and extracted with EtOAc. The organic layer is dried (Na_2SO_4) and concentrated. The residue is purified by flash chromatography (SiO_2, EtOAc) which furnished 160 mg (13%) of C-2 as a sticky foam. ^{1}H NMR 400 MHz ($CDCl_3$) δ 1.38, 2.49, 2.68, 2.73, 3.00, 3.42, 3.57, 3.78, 3.87, 4.05, 4.27, 4.68, 6.80, 7.13-7.30, 7.61; ^{13}C NMR ($CDCl_3$) δ 28.2, 33.2, 38.5, 52.1, 56.2, 58.2, 60.9, 62.8, 66.7, 71.9, 80.6, 114.6, 121.0, 126.9, 128.6, 128.9, 131.1, 131.5, 132.5, 134.1, 136.6, 156.2, 166.2, 169.0, 171.6. MS (ESI) 543 (M-H). Anal. Calcd for $C_{28}H_{36}N_2O_9$: C, 61.75; H, 6.66; N, 5.14. Found; C, 61.5; H, 6.6; N, 5.3.

PREPARATION OF C-3: 5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-hydroxypropyl]-2-(carboxymethoxy)benzoic acid: To a solution of C-2 (36 mg, 0.066 mmol) in THF (1.5 mL) was added a 2.5 M aqueous solution of LiOH (106 μL, 0.26 mmol). The mixture was stirred at room temperature for 4 h, and then acidified with 10% aqueous HCl and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated to afford 33 mg (96%) of C-3 as a white solid. Mp = 168.8-172.3 °C. ^{1}H NMR 400 MHz (MeOH) δ 1.35, 2.31, 2.64-2.97, 3.52, 4.06, 4.22, 4.78, 7.00, 7.11-7.27, 7.43, 7.77; ^{13}C NMR (MeOH) δ 20.7, 28.6, 30.9, 36.8, 39.5, 57.3, 67.5, 80.6, 111.0115.6, 121.3, 127.6, 129.3, 130.3, 133.6, 134.0, 136.1, 138.6, 157.5, 169.1, 172.2, 174.1. MS (ESI) 516 (M-H). Anal. Calcd for $C_{26}H_{32}N_2O_9 \cdot H_2O$: C, 59,42; H, 6.33; N, 5.33. Found; C, 59.4; H, 6.3; N, 5.35.4.

EXAMPLE 4: (Chart D, Formula D-5) 2-[4-[(2S)-2-({(2S)-2-[(Tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-(pentylamino)propyl]-2-(3-hydroxy-5-isoxazolyl)phenoxy]acetic acid

PREPARATION OF D-2: Methyl 2-{4-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-oxo-3-(pentylamino)propyl]-2-iodophenoxy}acetate:

Prepared from D-1 (2.24 g, 4.70 mmol) by the general method as described for A-4, which afforded 2.29 g (89%) of the title compound as a white solid. 1H NMR 400 MHz ($CDCl_3$) δ 0.88 (t, 3H, J = 7.1, 14.4), 1.20 (m, 2H), 1.29 (m, 2H), 1.38 (m, 2H), 1.43 (s, 9H), 2.96 (m, 2H), 3.17 (m, 2H), 3.81 (s, 3H), 4.19 (m, 1H), 4.67 (s, 2H), 5.06 (br s, 1H), 5.79 (br s, 1H), 6.63 (d, 1H, J = 8.4), 7.12 (dd, 1H, J = 2.1, 8.4), 7.64 (d, 1H, J = 2.1); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.3, 28.3, 28.9, 29.1, 37.2, 39.5, 52.4, 56.0, 66.3, 80.3, 86.6, 112.3, 130.4, 132.3, 140.5, 155.4, 155.7, 168.8, 170.6. MS (ESI) 544 (M-H). Anal. Calcd for $C_{22}H_{33}N_2O_6I$: C, 48.18; H, 6.06. Found: C, 48.3; H, 6.2.

PREPARATION OF D-3: Ethyl 3-[5-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-oxo-3-(pentylamino)propyl]-2-(2-methoxy-2-oxoethoxy)phenyl]-2-propynoate:

Ethyl propiolate (1.94 mL, 19.2 mmol) was added to a suspension of copper(I)oxide (0.61 g, 6.39 mmol) in anhydrous DMF (3 mL) under nitrogen atmosphere. A solution of D-2 (4.38 g, 7,99 mmol) in DMF (40 mL) was added. The reaction flask was flushed with nitrogen, tightly sealed, and stirred at 110 °C for 16 h. The reaction mixture was filtered through a short pad of SiO_2 and washed with EtOAc. The organic layer was washed with 1 M aqueous HCl (20 mL), brine (20 mL), saturated aqueous $NaHCO_3$ (20 mL), dried (Na_2SO_4) and concentrated. The

residue was purified by column chromatography (SiO_4, EtOAc/hexane 1:2 to 1:1) which afforded 1.93 g (47%) of D-3 as a white solid. Mp = 133.9-135.1 °C. ^{1}H NMR 400 MHz ($CDCl_3$) δ 0.87 (t, 3H, J = 7.1, 14.4), 1.22 (m, 2H), 1.29 (m, 2H), 1.35 (t, 3H, J = 7.1), 1.41 (s and m, 11H), 2.97 (app t, 2H, J = 6.7, 13.2), 3.17 (m, 2H), 3.80 (s, 3H), 4.21 (m, 1H), 4.29 (q, 2H, J = 7.1), 4.72 (s, 2H), 5.06 (br s, 1H), 5.91 (m, 1H), 6.70 (d, 1H, J = 8.6), 7.22 (dd, 1H, J = 2.1, 8.6), 7.38 (d, 1H, J = 2.1); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 22.2, 28.2, 28.9, 29.1, 37.4, 39.5, 52.3, 55.9, 62.0, 65.9, 80.3, 82.1, 85.0, 109.9, 112.6, 130.3, 133.0, 135.7, 154.0, 155.3, 158.8, 168.7, 170.6. MS (ESI) 517 (M-H). Anal. Calcd for $C_{27}H_{38}N_2O_8 \cdot H_2O$: C, 60.43; H, 7.33; N, 5.22. Found: C, 60.7; H, 7.4; N, 5.3.

PREPARATION OF D-4: Ethyl 3-[5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-(pentylamino)propyl]-2-(2-methoxy-2-oxoethoxy)phenyl]-2-propynoate:

Prepared from D-3 (1.01 g, 1.95 mmol) by the general method as described for A-5, which afforded 1.09 g (84%) of the title compound as a white solid. Mp = 121.8-123.1 °C. ^{1}H NMR 400 MHz ($CDCl_3$) δ 0.87 (t, 3H, J = 7.1, 14.4), 1.14-1.41 (m, 6H), 1.34 (t, 3H, J = 7.1), 1.35 (s, 9H), 2.81 (m, 1H), 3.01-3.09 (m, 4H), 3.15 (m, 1H), 3.77 (s, 3H), 4.27 (m, 1H), 4.29 (q, 2H, J = 7.1), 4.56 (m, 1H), 4.69 (s, 2H), 4.97 (d, 1H, J = 6.3), 6.17 (br m, 1H), 6.41 (br m, 1H), 6.66 (d, 1H, J = 8.6), 7.10-7.19 (m, 4H), 7.25-7.34 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 22.2, 28.1, 28.9, 36.4, 37.7, 39.6, 52.2, 53.6, 56.1, 62.0, 65.8, 80.6, 82.0, 85.0, 109.8, 112.6, 127.2, 128.8, 129.2, 129.9, 133.1, 135.5, 136.0, 153.9, 158.8, 168.6, 169.6, 170.9. MS (ESI) 664 (M-H). Anal. Calcd for $C_{36}H_{47}N_3O_9$: C, 64.95; H, 7.12; N, 6.31. Found: C, 64.9; H, 7.0; N, 6.3.

PREPARATION OF D-5: 2-[4-[(2S)-2-({(2S)-2-[(Tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-(pentylamino)propyl]-2-(3-hydroxy-5-isoxazolyl)phenoxy]acetic acid:

2.5 M aqueous NaOH (670 μL, 1.68 mmol) was added to hydroxylamine hydrochloride (61 mg, 0.87 mmol). This mixture was added to a solution of D-4 (446 mg, 0.67 mmol) in ethanol/THF (1 mL: 2mL). The clear yellow solution was stirred over night at ambient temperature, and then acidified with 1 M aqueous HCl. The reaction mixture was extracted with EtOAc (2x4 mL), and the organic layer was washed with brine (4 mL), dried (Na_2SO_4) and concentrated which afforded 418 mg of a crude material as a yellowish solid. This material was a mixture of the target compound and the corresponding hydroxamic acid analogs. Separation by reversed phase HPLC furnished 82 mg (19%) of pure title compound D-5 as a white solid. Melting point:

sublimented above 260 °C. Accurate mass: Calculated 638.2952; Found 638.2957. MS (ESI) 637 (M-H). Anal. Calcd for $C_{33}H_{42}N_4O_9\ H_2O$: C, 60.35; H, 6.75; N, 8.53. Found: C, 60.2; H, 6.6; N, 8.6.

EXAMPLE 5: (Chart E, Formula E-6) 2-[4-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-(pentylamino)propyl]-2-(2-hydroxy-3,4-dioxo-1-cyclobuten-1-yl)phenoxy]acetic acid

PREPARATION OF E-2: (2S)-2-amino-3-(4-hydroxy-3-iodophenyl)-N-pentylpropanamide (E-1) (8.64 g, 14.30 mmol) was dissolved in CH_2Cl_2 and stirred at 0 °C under N_2. Then EDC (2.74 g, 14.30 mmol), HOBt (1.93 g, 14.30 mmol) and Boc-L-Phe (3.79g, 14.30 mmol) were added simultaneously. Et_3N (3.98 mL, 28.6 mmol) was added dropwise. The resulting mixture was stirred overnight. EtOAc (200 mL) was added and the organic layer was washed with 5% aqueous HCl (2 x 100 mL). The aqueous phases were combined and extracted with EtOAc (100 mL). The combined organic phases were washed with 10% aqueous $NaHCO_3$, (100 mL). Drying (Na_2SO_4), filtration and evaporation of volatiles gave an yellowish solid. Column chromatography of the crude product on silica using $CHCl_3$/MeOH (95:5) and then EtOAc/light petroleum (1:1) as eluent gave 3.58 g 43% of a pale white solid: TLC Rf = 0.08 (SiO_2, $CHCl_3$/MeOH 99:1); Mp 162-164 °C. ^{1}H NMR ($CDCl_3$) δ 7.38–7.16 (m, 6H), 6.92-6.87 (m, 1H), 6.84 (d, J = 8.16 Hz, 1H), 6.28 (brs, 1H), 6.13 (brs, 1H), 6.0 (brs, 1H) 4.89 (d, J = 5.97 Hz, 1H), 4.57-4.50 (m, 1H), 4.29-4.23 (m, 1H), 3.20-2.95 (m, 5 H), 2.72-2.62 (m, 1H), 1.45-1.15 (m, 15H), 0.87 (tr, J = 7.22 Hz, 3H); ^{13}CNMR ($CDCl_3$) δ 170.80, 169.87, 155.73, 154.25, 138.82, 135.92, 131.09,130.09, 129.24, 128.97, 127.37, 115.19, 85.49, 80.89, 56.19, 53.53, 39.76, 37.59, 36.07, 28.99, 28.95, 28.10, 22.29, 13.94; IR (KBr disc) 1690, 1655 cm^{-1}; MS (ESI) m/z 624 (m+H),; Anal. Calcd for $C_{28}H_{38}IN_3O_5 \cdot 0.25\ H_2O$: C, 53.17; H, 6.06; N, 6.64; Found: C, 52.95; H, 5.95; N, 6.00.

PREPARATION OF E-3: A mixture of E-2 (463 mg 0.742 mmol), methyl bromoacetate (206 μL, 2.23 mmol) and K_2CO_3 (308 mg, 2.23 mmol) in CH_3CN (4 mL) was stirred at 40 °C overnight. The reaction mixture was filtered and the solid was washed with CH_3CN. The organic phase was concentrated to give a crude solid. The solid was dissolved in $CHCl_3$ and purified by column chromatography on SiO2 using EtOAc/pentane (1:1) as eluent to give 0.446 g (86%) of the product as a white solid: TLC Rf = 0.11 (SiO_2, $CHCl_3$/MeOH 99:1); Mp 141-142 °C. ^{1}H NMR ($CDCl_3$) δ 7.45–7.25 (m, partly obscured by solvent signal, 6H), 7.02 (m, 2H), 7.02 (d,d,

J = 1.89 and 8.48 Hz, 1H) 6.60 (d, J = 8.48 Hz, 1H), 6.24 (brs, 1H), 610 (brs, 1H), 4.83 (m, 1H). 4.64 (s, 2H), 4.57-4.47 (m, 1H), 4.30-4.21 (m, 1H), 3.79 (s, 3H), 3.20-2.95 (m, 5H), 2.78-2.70 (m, 1H), 1.43-1.15 (m, 15H), 0.87 (tr, J = 7.22 Hz, 3H); ^{13}C NMR ($CDCl_3$)
δ 170.74, 169.65, 168.59, 155.90, 140.35, 135.97, 131.82, 130.43, 129.21, 128.97, 128.85, 127.3
5 5, 112.44, 86.54, 80.83, 66.34, 56.27, 53.54, 52.28, 39.71, 39.58, 37.65, 36.14, 28.99, 28.95, 28. 12, 22.27 ; IR (KBr disc) 1690, 1645 cm^{-1}; MS (ESI) m/z 694 (m-H),; Anal. Calcd for $C_{31}H_{42}IN_3O_7$: C, 53.53; H, 6.09; N, 6.04; Found: C, 53.40; H, 6.15; N, 6.00.

PREPARATION OF E-4: A mixture of E-3 (508.0 mg 0.7303 mmol), 3-isopropoxy-4-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-dione (prepared from 3,4-diisopropoxycyclobutenediones
10 using the protocol of Liebeskind, L.S.; Fengl, R.W., *J. Org. Chem.*, **1990**, 55, 5359-5364. 313.4 mg, 0.7303 mmol), $Pd_2(dba)_3$ (16.7 mg, 0.0292 mmol), and $AsPh_3$ (35.8 mg, 0.1168 mmol) in degassed DMF was stirred at room temperature. After 5 min, CuI (11.12 mg, 0.058 mmol), and the mixture was stirred at 50 °C for 24 h. Additional $Pd_2(dba)_3$ (16.7 mg, 0.0292 mmol), and $AsPh_3$ (35.8 mg, 0.1168 mmol), CuI (11.12 mg, 0.058 mmol) were added and the reaction was
15 run for another 48 h. The reaction mixture was diluted with EtOH (10 mL) and filtered through celite. The mixture was concentrated and partioned between water and $CHCl_3$. The organic phase was filtered and concentrated. The crude residue was purified by flash chromatography on silica by first using gradient elution ($CHCL_3$→ $CHCL_3$/MeOH) and then by using $CHCL_3$ + 2.5% MeOH. This gave 215 mg (44%) of the product as yellowish solid: TLC Rf = 0.1 (SiO_2,
20 $CHCl_3$/MeOH 99:1); Mp 175-178 °C. ^{1}H NMR ($CDCl_3$) δ 7.74-7.71 (m, 1H) 7.35-7.16 (m., partly obscured by solvent signal, 7H), 6.78 (d, J = 8.48 Hz, 1H), 6.57-6.50 (m, 1H), 5.65 (h, J = 6.28 Hz, 1H), 5.46 (brs, 1H), 4.68 (d, J = 3.77 Hz, 2H), 4.28-4.23 (m, 1H), 3.79 (s, 3H), 3.26-2.86 (m, 7H), 1.49 (d, J = 6.28 Hz, 6H), 1.45-1.17 (m, 15H), 0.87 (tr, J = 7.22 Hz, 3H); ^{13}C NMR ($CDCl_3$)
25 δ 194.23, 193.12, 193.03, 171.91, 171.28, 169.74, 168.33, 154.28, 136.53, 135.15, 130.28, 129.7 3, 129.24, 128.75, 128.68, 127.01, 117.77, 113.11, 79.44, 65.71, 57.04, 52.26, 39.75, 37.54, 28.9 1, 28.12, 28.03, 22.90, 22.26, 13.91. not all signals are visible in the ^{13}C NMR spectrum; IR (KBr disc) 3291, 1644 cm^{-1}; MS (ESI) m/z 694 (M-isopropyl); HPLC: chemical purity 90.6%; Anal. Calcd for $C_{38}H_{49}N_3O_{10}$ 1.0 H_2O: C, 62.88; H, 7.08; N, 5.78; Found: C, 62.85; H, 6.90; N,
30 5.90.

PREPARATION OF E-5: E-4 was dissolved in warm THF (10 mL) . 6M aqueous HCl (0.5 mL) was added and the solution was stirred at room temperature 3 days and then at 50 °C

for 2h . The reaction mixture was concentrated to give 1.48 g of a yellow solid. The solid was triturated first with ether then with acetone/water to give 503 mg of a yellow solid. The solid was then purified on a reverse phase preparative HPLC system to give 406 mg (71%) of the pure compound: Mp 210-decomp. ^{1}H NMR (DMSO-*d6*) δ 15.14 (brs, 1H), 8.75 (d, *J* = 8.48 Hz, 1H), 8.16 (d, *J* = 2.20 Hz, 1H), 8.03 (m, 3H), 7.35-7.13 (m, 5H), 6.97 (d, *J* = 8.48 Hz, 1H), 4.69 (s, 2H), 4.48 (m, 1H), 4.10 (m, 1H), 3.15-2.70 (m, 5H), 1.40-1.10 (m, 5H), 0.83 (tr, *J* = 7.54 Hz, 3H); ^{13}C NMR (DMSO-*d6*)

δ 210.87, 196.94, 172.81, 169.68, 169.42, 167.72, 155.16, 151.39, 139.50, 134.79, 131.26, 129.48, 128.40, 127.01, 126.67, 120.82, 111.76, 65.53, 54.39, 53.23, 38.46, 37.31, 36.95, 28.58, 28.53, 21.74, 13.80; MS (ESI) m/z 552 (M+H); HPLC: 97% chemical purity.

PREPARATION OF E-6: To a stirred solution of E-5 (386.4 mg, 0.657 mmol), in 1M NaOH (3mL), dioxane (5mL) and water (4mL) was added di-*t*-butyldicarbonate at 0 °C. The reaction mixture was then stirred for 10 h. The mixture was acidified with 2M $KHSO_4$, and the dioxane was evaporated (precipitation of starting material). The reaction mixture was filtered and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated. The purity of the crude residue on a reversed phase HPLC system shows a purity of 64% with no major side products. Ms (ESI) shows the right molecular ion 650 (M-H). The solid was then purified on a reverse phase preparative HPLC system using the same conditions as in the analytical experiment (mobile phase CHCN/aq. 0.1% TFA gradient 10:90→95:5). An analytical sample was then run on the purest fraction (96% purity). Something happens with the product during workup. The worked up fraction seem to be more impure than the crude fraction. The workup consisted of carefully evaporate the organic phase and then lyophilize the product. The product seem to be very sensitive towards TFA.

EXAMPLE 6: (Chart F, R = pyridine, Formula F-2) Methyl 2-(2-methoxy-2-oxoethoxy)-5-{(2S)-3-oxo-3-(pentylamino)-2-[(3-pyridinylcarbonyl)amino]propyl}benzoate

PREPARATION OF F-2 (General Procedure A: Amide Coupling): Triethylamine was added dropwise to a stirred solution of F-1 (200mg, 0.44mmol) in dichloromethane (3.3ml) at 0°C until neutral. EDC (85mg, 0.44mmol), HOBT (60mg, 0.44mmol) and nicotinic acid (47mg, 0.44mmol) were then added in single portions to the stirred solution again at 0°C under nitrogen. The mixture was then allowed to warm to room temperature where it was stirred for 3hr. The yellow mixture was then diluted with EtOAc (20ml) and the organic solution washed with HCl

(2M, 10ml). The acidic layer was basified with NaOH and extracted with EtOAc (3 x 10ml) and the combined organic layers washed with $NaHCO_3$ (1 x 10ml), dried ($MgSO_4$) and concentrated under reduced pressure to give a cloudy oil. The crude product was purified by column chromatography on silica gel using petrol:EtOAc:MeOH (4:2:1) as eluent to give a white solid, F-2 (120mg), ^{1}H NMR (270MHz, MeOH) δ 8.90 (1H, s), 8.66 (1H, d, J = 4.95 Hz), 8.15 (1H, dt, J = 2.31, 8.04Hz),7.72 (1H, d, J = 2.31Hz), 7.51 (1H, dd, J = 4.95, 7.92Hz), .7.41 (1H, dd, J = 2.31, 6.27Hz), 6.93 (1H, d, J = 8.58Hz), 4.75 (2H, s), 4.73 (1H, obscured m), 3.83 (3H, s), 3.74 (3H, s), 3.58-2.97 (4H, m), 1.45-1.20 (6H, m), 0.88 (3H, t, J = 6.93Hz).

EXAMPLE 7: (Chart F, R = pyridine, Formula F-3) 5-[(2S)-2-({(2R)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl} amino)-3-oxo-3-(pentylamino)propyl]-2-(carboxymethoxy)benzoic acid dihydrochloride

PREPARATION OF F-3 (General Procedure B: Ester Hydrolysis): Lithium hydroxide (15mg, 0.64mmol) was added to a stirred solution of F-2 (100mg, 0.21mmol) in THF (20ml) and the mixture stirred at room temperature for 3hr. The solvent was removed in vacuo and the residue dissolved in water (20ml) and acidified with HCl (10% aqueous). The solution became cloudy and was extracted with EtOAc (3 x 10ml). The combined organic phases were dried ($NaSO_4$) and concentrated under reduced pressure to give a white solid F-3 (40mg, 0.09mmol, 42%) m.p. 168-170°C; υ_{max}(cm^{-1}) 3288, 3073, 2931, 1731, 1639, 1545, 1498; ^{1}H NMR (500MHz, DMSO) δ 8.96 (1H, s), 8.80 (1H, d, J = 8.17Hz), 8.71 (1H, br s), 8.16 (1H, d, J = 7.85 Hz), 8.08 (1H, t, J = 5.65Hz), .7.70 (1H, d, J = 2.20Hz), 7.5o (1H, dd, J 4.71, 7.85Hz), 7.43 (1H, dd, J 2.51, 8.79Hz), 6.92 (1H, d, J = 8.47Hz), 4.70 (2H, s), 4.64-4.55 (1H, m), 3.12-3.01 (4H, m), 1.44-1.16 (6H, m), 0.85 (3H, t, J = 7.22Hz); ^{13}C NMR (500MHz, CD_3OD) 172.90, 167.81, 157.65, 152.58, 149.00, 137.36, 136.06, 133.87, 132.10, 115.83, 67.95, 56.76, 40.51, 37.95, 30.89, 30.02, 29.80, 23.25, 14.30; MS (ESI) 456.2 ($M-H^+$), 458.2 ($M+H^+$).

EXAMPLE 8: (Chart F, R = 2-methoxybenzyl, Formula F-5) 2-(carboxymethoxy)-5-[(2R)-2-{[2-(2-methoxyphenyl)acetyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid

(a) PREPARATION OF F-4: Methyl 2-(2-methoxy-2-oxoethoxy)-5-[(2R)-2-{[2-(2-methoxyphenyl)acetyl]-amino}-3-oxo-3-(pentylamino)propyl]benzoate:

By general procedure A, a solution of F-1 (500mg, 1.2mmol) in dichloromethane (8ml) was treated with EDC (230mg, 1.2mmol), HOBT (162mg, 1.2mmol), triethylamine (243mg,

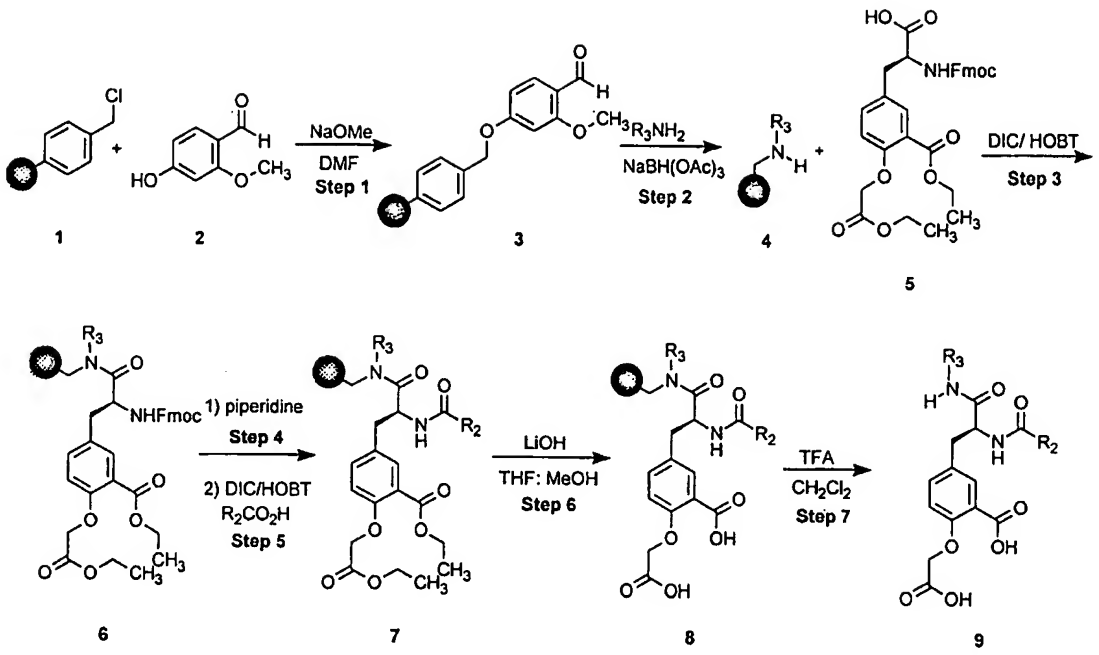
2.4mmol) 2-(2-methoxyphenyl)acetic acid (199mg, 1.2mmol) at room temperature overnight. The mixture was then diluted with EtOAc (20ml) and the organic layer washed with HCl (5%, 1x15ml). The aqueous layer was then extracted with EtOAc (3x10ml) and the combined organic layers washed with $NaHCO_3$ (sat. aq.), dried ($MgSO_4$) and concentrated to give a yellow oil. The crude product was purified by column chromatography using dichoromethane:MeOH (20:1) as eluent to give a white solid, F-4 (320mg, 0.6mmol, 50%) m.p. 145-6; $\upsilon_{max}(cm^{-1})$.3282, 2954, 1755, 1731, 1642, 1547, 1497, 1437; ^1H NMR (500MHz, CD_3OD) δ 7.57 (1H, d, *J* = 2.2Hz), 7.24-7.19 (2H, m), 7.08 (1H, d, *J* 7.22Hz), 6.92-6.84 (3H, m), 4.75 (2H, s) 4.52 (1H, m), 3.85 (3H, s), 3.77 (3H, s), 3.74 (3H, s), 3.52 (1H, d (AB), *J* = 14.76Hz), 3.45 (1H, d (AB), *J* = 14.76Hz), 3.16-3.03 (2H, m), 3.00 (1H, dd, *J* 6.6, 14.3Hz), 2.86 (1H, dd, *J* 7.84, 13.82Hz), 1-43-1.17 (6H, m), 0.88 (3H, t, *J* 7.22Hz); ^{13}C NMR (500MHz, CD_3OD) δ 173.83, 172.80, 170.84, 168.04, 158.75, 157.76, 135.45, 133.36, 131.87, 131.36, 129.72, 124.75, 121.87, 121.76, 115.38, 111.80, 67.09, 55.96, 55.74, 52.60, 52.52, 40.44, 38.69, 38.17, 30.11, 29.93, 23.33, 14.29; MS (ESI) 529.1 ($M+H^+$); Anal. Calculated for C28H36N2O8: C, 63.6; H, 6.9; N, 5.3; Found: C, 63.6; H, 6.9; N, 5.3%.

(b) PREPARATION OF F-5:

By general procedure B, a solution of F-4 (280mg, 0.53mmol) in THF (5ml) and water (5ml) was treated with lithium hydroxide (100mg, 1.1mmol) at room temperature overnight. The crude product was recrystallised from acetonitrile to give a white crystalline solid, F-5 (130mg, 0.26mmol, 50%) m.p. 146-8°C; $\upsilon_{max}(cm^{-1})$.3296, 2929, 1736, 1643, 1547, 1495; ^1H NMR (500MHz, CD_3OD) δ 7.71 (1H, br d, *J* = 6.2Hz), 7.23 (2H, m), 7.09 (1H, d, *J* = 7.04Hz), 6.93-6.86 (3H, m), 4.79 (2H, s), 4.55 (1H, br t, *J* = 7.45Hz), 3.75 (3H, s), 3.55 (1H, d (AB), *J* = 14.48Hz), 3.45 (1H, d (AB), *J* = 15.3Hz), 3.18-3.06 (2H, m), 3.02 (1H, dd, *J* = 6.20, 14.07Hz), 2.87 (1H, dd, *J* = 7.45, 13.66Hz), 1.44-1.20 (6H, m), 0.88 (3H, t, *J* = 7.45Hz); ^1H NMR (500MHz, CD_3OD) δ 172.84, 172.75, 172.20, 168.96, 158.71, 157.73, 135.99, 134.03, 131.88, 131.84, 129.77, 124.70, 121.79, 121.30, 115.50, 111.84, 67.41, 55.98, 55.67, 40.45, 38.70, 38.19, 30.11, 29.94, 23.32, 14.29; MS (ESI) 499.0 ($M-H^+$); Anal. Calculated for $C_{26}H_{32}N_2O_8$: C, 62.4; H, 6.4; N, 5.6; Found: C, 62.2; H, 6.4; N, 5.6%.

EXAMPLE 9: Two-dimensional library of 5-substituted-2-carbomethoxybenzoic acids

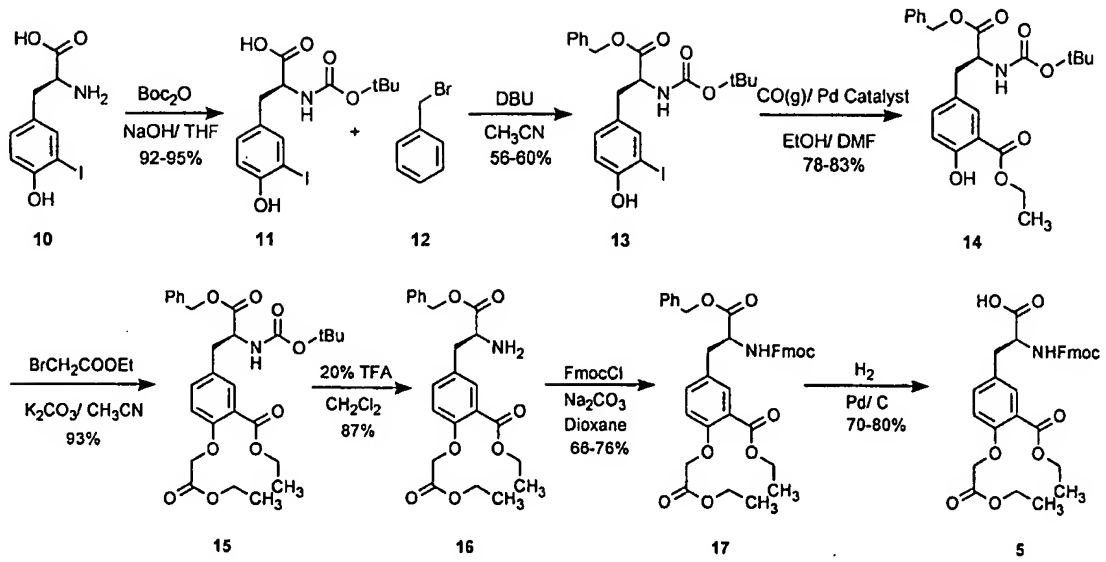
Scheme 1



Chemistry Summary

The combination solid-phase/solution-phase synthetic sequence was designed to prepare a 6x11 two-dimensional library of 5-substituted-2-carboxymethoxybenzoic acids in a 96-well format as illustrated in Scheme 1. The synthesis was based on the use of the AMEBA linker (acid sensitive methoxybenzaldehyde, **3**), selected due to its ease of cleavage and versatility in the reductive amination step. The intermediate **5** was synthesized in a seven step sequence described in "Intermediate Synthesis" below. The key resin **3** was synthesized by treating Merrifield resin with 2-methoxy-4-hydroxybenzaldehyde according to the literature procedure (Fivush, A.M.; Willson, T.M. *Tetrahedron Lett.* **1997**, *38*, 7151. Sarantakis, D.; Bicksler, J.J. *Tetrahedron Lett.*, **1997**, *38*, 7325). The functionalized resin **3** was treated with the first diversity element, a primary amine, and sodium triacetoxyborohydride to provide six different secondary amine resins, **4**. Attachment of **5** to each individual resin was performed utilizing the standard conditions of DIC/HOBt in DMF. A deprotection/ condensation protocol was followed to attach the next diversity element to give **7**. Hydrolysis of the diester was then followed by removal of the products from the resin with 20% TFA/CH_2Cl_2.

Scheme 2 - Intermediate Synthesis



The tyrosine scaffold (**5**) was prepared in seven steps with an overall yield of 23% on a multi-gram scale. Commercially available 3-iodotyrosine (**10**) was treated with di-t-butylcarbonate to afford **11** (92-95%), treatment of **11** with DBU (1,5-diazobicyclo[5.4.0.]-undec-5-ene) and benzyl bromide (**12**) gave **13** (56-60%). Carbonylation of **13** in ethanol gave the corresponding ethyl ester **14** in 93% yield. Treatment of **14** with ethyl bromoacetate in potassium carbonate gave the diethyl ester **15** (93%). Deprotection of the Boc group was carried out using 20% TFA to afford the amine **16** (87%), which was protected with Fmoc-Cl to give **17** (66-76%), followed by hydrogenation to afford the acid **5** (70-80%).

(2S)-2-[(*tert*-Butoxycarbonyl)amino]-3-(4-hydroxy-3-iodophenyl)propanoic Acid (11) To a solution of 3-iodo-L-tyrosine (**10**) (5.00 g, 16.3 mmol) in 1.0 M NaOH (16.3 mL), H_2O (16 mL) and THF 32 mL was added di-*tert*-butyl dicarbonate (3.95 g, 18.1 mmol). After 1.5 hr at rt, the reaction was concentrated *in vacuo* to remove THF, diluted with H_2O (25 mL), and washed with Et_2O (3 x 25 mL). The aqueous phase was brought to pH 4 with 1 M citric acid, extracted with CH_2Cl_2 (3 x 50 mL), and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded **11** (6.30 g, 95%) as a white foam (Rzeszotarska, B.; Nadolska, B.; Tarnawski, J. *Liebigs Ann. Chem.* **1981**, *7*, 1294). ^{1}H NMR (300 MHz, DMF-d_7) δ 7.67 (s, 1 H), 7.18 (d, J = 8 Hz, 1 H), 6.92 (d, J = 8 Hz, 1 H), 4.29-4.24 (m, 1 H), 3.08 (dd, J = 9, 14 Hz, 1 H), 2.88-2.84 (m, 1 H), 1.37 (s, 9 H).

Benzyl (2S)-2-[(tert-Butoxycarbonyl)amino]-3-(4-hydroxy-3-iodophenyl)propanoate (13). A solution of acid **11** (17.6 g, 43.3 mmol) in 150 mL of CH_3CN was treated DBU (6.8 mL, 45

mmol) and benzylbromide (**12**) (5.4 mL, 45 mmol). The reaction mixture was stirred at rt for 18 h, then concentrated to remove CH_3CN, diluted with 300 mL of CH_2Cl_2, washed with 1 N HCl (2x 150 mL), 100 mL of water, dried over $NaSO_4$ and condensed. Purified by chromatography (20% EtOAc: Heptane) to yield **13** as an oil (21.5 g, 24.3 mmol, 56% yield). UV λ_{max} 228 (10800, 95% ETHANOL); ^{1}H NMR ($CDCl_3$) δ 7.41-7.31 (m, 6 H), 6.88 (d, J = 8 Hz, 1 H), 6.79 (d, J = 8 Hz, 1 H), 5.95 (br s, 1 H), 5.22-5.10 (m, 3 H), 4.59-4.13 (m, 1 H), 3.02-2.96 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 155.2, 154.2, 139.1, 135.0, 131.0, 129.8, 128.7, 128.6, 115.1, 85.4, 80.3, 67.3, 54.6, 36.9, 28.4; IR (drift) 3457, 3362, 1737, 1683, 1528, 1503, 1350, 1294, 1281, 1206, 1195, 1169, 810, 753, 701 cm^{-1}; MS (EI) *m/z* 497 (M^+), 380, 233, 107, 106, 92, 91, 77, 65, 57, 51. Anal. Calcd for $C_{21}H_{24}INO_5$: C, 50.72; H, 4.86; N, 2.82. Found: C, 50.87; H, 4.70; N, 2.72.

Ethyl 5-{(2S)-3-(Benzyloxy)-2-[(tert-butoxycarbonyl)amino]-3-oxopropyl}-2-hydroxybenzoate (14) A solution of **13** (12.1 g, 24.3 mmol) in 50 mL of EtOH and 120 mL of DMF was treated with Pd(II)Acetate (270 mg, 1.20 mmol), triethylamine (6.8 mL, 48.8 mmol). The reaction atmosphere was replaced with CO (g) at 1 atm. and stirred at 60-70°C for 18 h. The reaction mixture was diluted with 300 mL of EtOAc, washed with 1 N HCl (3x 100 mL) and 100 mL of water. The organics were dried over Na_2SO_4 and condensed. Purified by chromatography (20% EtOAc: heptane) to give product **14** as white crystals (8.44 g, 19.0 mmol, 78%yield). UV λ_{max} 228 (10800, 95% EtOH); ^{1}H NMR ($CDCl_3$) δ 10.73 (s, 1 H), 7.61 (d, J = 2 Hz, 1 H), 7.38-7.36 (m, 3 H), 7.32-7.28 (m, 2 H), 7.11 (br d, J = 8 Hz, 1 H), 6.84 (d, J = 8 Hz, 1 H), 5.18 (d, J = 12 Hz, 1 H), 5.13 (d, J = 12 Hz, 1 H), 5.06 (br d, 1 H), 4.62-4.59 (m, 1 H), 4.39 (q, J = 7 Hz, 2 H), 3.09-3.00 (m, 2 H), 1.43 (s, 9 H), 1.41 (t, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.0, 160.7, 155.0, 136.6, 135.0, 130.4, 128.6, 128.6, 128.5, 126.5, 117.8, 112.5, 80.0, 67.2, 61.5, 54.5, 37.4, 28.3, 14.2; IR (drift) 3357, 1732, 1687, 1528, 1493, 1371, 1292, 1270, 1252, 1207, 1191, 1169, 1088, 792, 699 cm^{-1}; MS (EI) *m/z* 443 (M^+), 326, 180, 179, 134, 133, 91, 77, 65, 57, 51. Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.93; H, 6.48; N, 3.11.

Ethyl 5-{(2S)-3-(Benzyloxy)-2-[(tert-butoxycarbonyl)amino]-3-oxopropyl}-2-(2-ethoxy-2-oxoethoxy)benzoate (15) A solution of **14** (5.76 g, 13.0 mmol) in 100 mL of CH_3CN was treated with solid K_2CO_3 (9.0 g, 65.1 mmol), ethylbromoacetate (1.7 mL, 15.3 mmol). The

reaction mixture was stirred at rt for 14 h, additional ethylbromoacetate (0.5 mL, 4.5 mmol) added, then refluxed for 1 h. The reaction solution was filtered to remove K_2CO_3 with fine filter paper to yield **15** as an orange oil. Purified by chromatography (20% EtOAc/ heptane) to yield a clear colorless oil (6.37 g, 12.0 mmol, 93%). $[\alpha]^{25}_D = 5°$ (*c* 0.78, chloroform); UV λ_{max} 228 (10800, 95% EtOH); ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 1 H), 7.36-7.28 (m, 5 H), 7.10 (d, *J* = 8 Hz, 1 H), 6.74 (d, *J* = 8 Hz, 1 H), 5.12 (d, *J* = 2 Hz, 2 H), 5.06 (d, *J* = 9 Hz, 1 H), 4.64 (s, 2 H), 4.60-4.57 (m, 1 H), 4.34 (q, *J* = 7 Hz, 2 H), 4.25 (q, *J* = 7 Hz, 2 H), 3.10-3.01 (m, 2 H), 1.40 (s, 9 H), 1.36 (t, *J* = 7 Hz, 3 H), 1.27 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 168.5, 165.6, 156.6, 155.0, 135.1, 134.0, 132.6, 129.4, 128.6, 128.5, 121.5, 114.7, 79.9, 67.2, 66.9, 61.3, 60.9, 54.4, 37.2, 31.9, 28.3, 22.7, 14.2; IR (liq.) 2980, 1717, 1500, 1456, 1446, 1392, 1379, 1367, 1303, 1254, 1200, 1166, 1090, 1068, 1022 cm^{-1}; MS (EI) *m/z* 529 (M^+), 266, 265, 220, 192, 179, 133, 91, 59, 57, 56. Anal. Calcd for $C_{28}H_{35}NO_9$: C, 63.50; H, 6.66; N, 2.64. Found: C, 63.86; H, 6.76; N, 2.63.

Ethyl 5-[(2S)-2-Amino-3-(benzyloxy)-3-oxopropyl]-2-(2-ethoxy-2-oxoethoxy)benzoate (16) A solution of **15** (10.0 g, 18.9 mmol) in 100 mL of 20% TFA/ CH_2Cl_2 was stirred at rt for 2 h. The reaction mixture was condensed; the oil was redissolved in 400 mL of CH_2Cl_2 and washed with $NaHCO_3$ and dried over $NaSO_4$, condensed to yield product **16** as an oil (8.12 g, 17.0 mmol, 90% yield). $[\alpha]^{25}_D = -3°$ (*c* 0.52, methanol); UV λ_{max} 227 (9410, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2 Hz, 1 H), 7.32 (m, 6 H), 6.78 (d, 1 H), 5.14 (s, 2 H), 4.66 (s, 2 H), 4.35 (q, *J* = 7 Hz, 2 H), 4.26 (q, *J* = 7 Hz, 2 H), 3.75 (dd, *J* = 6, 8 Hz, 1 H), 3.05 (dd, *J* = 5, 14 Hz, 2 H), 2.87 (dd, *J* = 8, 14 Hz, 2 H), 1.38 (t, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.6, 169.3, 166.7, 156.7, 136.0, 138.4, 132.1, 130.4, 128.6, 128.4, 128.3, 121.5, 114.6, 66.7, 66.3, 61.3, 61.2, 55.7, 39.7, 13.6, 13.5; IR (liq.) 2982, 1757, 1731, 1500, 1455, 1445, 1367, 1302, 1254, 1200, 1172, 1091, 1023, 754, 700 cm^{-1}; MS (FAB) *m/z* (rel. intensity) 430 (MH^+, 4), 430 (4), 265 (4), 133 (7), 92 (8), 91 (99), 81 (4), 69 (8), 55 (5), 41 (4), 29 (4). HRMS (FAB) calcd for $C_{23}H_{27}NO_7$+H_1 430.1866, found 430.1860.

Ethyl 5-((2S)-3-(Benzyloxy)-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}-3-oxopropyl)-2-(2-ethoxy-2-oxoethoxy)benzoate (17) A solution of **16** (6.93 g, 16.1 mmol) in 50 mL of dioxane was treated with Na_2CO_3 (5.47g 44.1 mmol) and 44 mL of water and then cooled to 0°C. To the cooled reaction mixture was added 9-fluorenylcarbonylchloride (4.57 g, 17.7 mmol)

portionwise. After 30 min the reaction mixture was warmed to rt for 5 h. The reaction mixture was concentrated to remove dioxane, then partitioned between water and CH_2Cl_2, organics dried over Na_2SO_4, and condensed. Purified by chromatography (20% EtOAc/ heptane to 50% EtOAc/ heptane) to yield **17** as a gummy clear oil (6.97 g, 10.7 mmol, 66% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8 Hz, 2 H), 7.63 (s, 1 H), 7.59 (t, J = 6 Hz, 1 H), 7.36 (m, 9 H), 7.08 (d, J = 8 Hz, 1 H), 6.75 (d, J = 9 Hz, 2 H), 5.38 (d, J = 8 Hz, 1 H), 5.17 (s, 2 H), 4.72 (m, 1 H), 4.65 (s, 2 H), 4.36 (m, 4 H), 4.24 (q, J = 9 Hz, 2 H), 4.21 (m, 1 H), 3.11 (m, 2 H), 1.35 (t, J = 7 Hz, 3 H), 1.27 (t, J = 5 Hz, 3 H).

(2S)-3-[3-(Ethoxycarbonyl)-4-(2-ethoxy-2-oxoethoxy)phenyl]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propanoic acid (5) To **17** (6.97 g, 10.7 mmol) was added 504 mg of Pd/C followed by the addition of 250 mL of MeOH. The reaction mixture was stirred at rt under 1 atm of H_2 (g) for 18 h. The reaction mixture was filtered through celite, condensed. Purified by chromatography (1% AcOH, 5% MeOH, CH_2Cl_2) to yield **5** as a white solid (4.19 g, 7.45 mmol, 70% yield). The product can be recrystallized in toluene/ heptane. $[\alpha]^{25}_D$ = 3° (c 0.99, methanol); UV λ_{max} 264 (18800, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 7.75 (d, J = 7 Hz, 2 H), 7.67 (s, 1 H), 7.55 (t, J = 8 Hz, 2 H), 7.39 (t, J = 7 Hz, 2 H), 7.24 (m, 3 H), 7.22 (m, 1 H), 6.79 (d, J = 8 Hz, 1 H), 5.41 (d, J = 8 Hz, 1 H), 4.68 (m, 1 H), 4.64 (s, 2 H), 4.26 (m, 6 H), 3.20 (m, 1 H), 3.08 (m, 1 H), 1.34 (t, J = 7 Hz, 3 H), 1.27 (t, J = 7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 168.6, 166.1, 156.5, 155.8, 143.7, 141.2, 134.1, 132.6, 129.1, 127.7, 127.1, 125.0, 121.6, 119.9, 114.6, 67.2, 66.8, 61.4, 61.2, 54.5, 47.1, 36.7, 14.2, 14.1; IR (drift) 3337, 3318, 1754, 1744, 1694, 1543, 1445, 1295, 1269, 1255, 1203, 1167, 1090, 764, 741 cm^{-1}; HRMS (FAB) calcd for $C_{31}H_{31}NO_9$+H_1 562.2077, found 562.2070.

Diversity Elements

N-Terminal Carboxylic Acids (commercially available):

Name	Cpd #
nicotinic acid	**18**
2-pyrazinecarboxylic acid	**19**

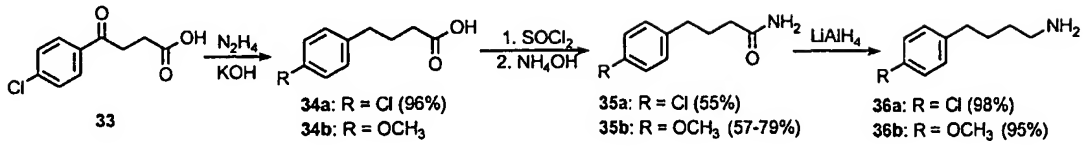
4-chlorobenzoic acid	**20**
6-chloronicotinic acid	**21**
2,3,5,6-tetrafluorobenzoic acid	**22**
5-methoxyindole-2-carboxylic acid	**23**
3-furoic acid	**24**
5,6-dichloronicotinic acid	**25**
cycloheptanecarboxylic acid	**26**
benzoic acid	**27**
N-acetyl-(L)-phenylalanine	**28**
(S)-(-)-3-(benzyloxycarbonyl)-4-oxazolidinecarboxylic acid	**29**

C-Terminal Amines:

a) Commercially available:

Name	Cpd #
n-propylamine	**30**
n-amylamine	**31**
4-phenylbutylamine	**32**

b) Synthesized:



33

34a: R = Cl (96%)
34b: R = OCH_3

35a: R = Cl (55%)
35b: R = OCH_3 (57-79%)

36a: R = Cl (98%)
36b: R = OCH_3 (95%)

Three of the six amines used in this library were commercially available, the remaining three amines **36a, 36b** and **38** were prepared synthetically. Wolff-Kishner reduction of 4-(p-

chlorophenyl)-4-oxobutanoic acid gave 4-(p-chlorophenyl)butanoic acid (**34a**) in 96% yield, which was converted to **35a** (55%). 4-(p-Methoxyphenyl)butylamine (**36b**) was similarly synthesized with equal results from commercially available **34b**. Benzyl ethylamine ether (**38**) was prepared in one step from ethanolamine and benzyl chloride in 10% yield.

4-(p-chlorophenyl)butanoic acid (34a)

A mixture of 3-(4-chlorobenzoyl) propionic acid (**33**) (2.50 g, 12.0 mmol), KOH (s) (1.75 g, 31.2 mmol), and hydrazine monohydrate (1.25 mL, 25.8 mmol) in 12.5 mL of diethylene glycol was refluxed azeotropically at 120-130°C for 90 min to remove water. The reaction mixture was then refluxed at 170°C for 3 h, cooled to RT, diluted with 12.5 mL of water, and poured into 15 mL 2.5 N HCl(aq). The precipate was filtered off, dissolved in CH_2Cl_2, and the solvent removed to give **34a** (2.23 g, 96%) as a white solid. UV λ_{max} 223(8980, 95% ETHANOL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7 Hz, 2 H), 7.12 (d, J = 8 Hz, 2 H), 2.66 (t, J = 4 Hz, 2 H), 2.38 (t, J = 4 Hz, 2 H), 1.96 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 179.3, 140.0, 132.2, 130.2, 128.9, 34.7, 33.4, 26.4; IR (drift) 3063 (s), 3051 (s), 2955 (s), 2923 (s,b), 2905 (s), 2814, 2797, 2493 (b), 2466, 2413, 2367 (b), 2321, 1706 (s), 1492 (s), 1212 (s), cm $^{-1}$; MS (EI) m/z (rel. intensity) 198 (M+, 22), 200 (7), 198 (22), 140 (32), 139 (17), 138 (99), 127 (15), 125 (48), 103 (10), 89 (13), 60 (9); HRMS (EI) calcd for 198.0448, found 198.0441.

4-(p-chlorophenyl)butanamide (35a)

A mixture of **34a** (1.880 g, 10.1 mmol) and thionyl chloride (3.0 mL, 40.9 mmol) in 15 mL $CHCl_3$ was stirred at reflux (75°C) for 4 h. Solvent and excess thionyl chloride were removed *in vacuo*, and residue was twice diluted with 7.5 mL toluene and evaporated to remove traces of thionyl chloride. To a solution of the residue in 3 mL toluene was slowly added 9 mL of cold concentrated NH_4OH. The precipitate was filtered off and recrystallized in $CHCl_3$/heptane to give **35a** (1.02 g, 55%) as a white solid. UV λ_{max} 224 (9300, 95% ETHANOL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8 Hz, 2 H), 7.12 (d, J = 8 Hz, 2 H), 5.31 (s, 2H), 2.66 (t, J = 8 Hz, 2 H), 2.23 (t, J = 7 Hz, 2 H), 1.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 140.2, 134.5, 130.2, 128.9, 35.1, 34.8, 27.0; IR (drift) 3434, 2948, 2282 (w), 1901 (w), 1655 (s), 1607, 1491, 1420, 1306, 1094, 1016, 836 (s), 825, 804, 666, cm^{-1}. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09; Cl, 17.94. Found: C, 60.60; H, 6.11; N, 6.96.

4-(p-chlorophenyl)butylamine (36a) (Ali, F.E.; Dandridge, P.A.; Gleason, J.G.; Krell, R.D.; Kruse, C.H.; Lavanchy, P.G; Snader, K.M. *J. Med. Chem.*, **1982**, *25*, 947)

To a stirred suspension of lithium aluminum hydride (2.40 g, 63.2 mmol) in 65 mL diethyl ether was added slowly a solution of (3.12 g 15.8 mmol) of **35a** in 28 mL THF, and stirred at rt for 1 h. To the reaction mixture was slowly added 4 mL water, 4 mL 5 N NaOH(aq), and 12 mL water. The organics were removed from the emulsion which was dissolved in water and extracted with ether. The organic portions were dried over Na_2SO_4(s), and condensed to give **36a** (2.76 g, 95%) as an oil. UV λ_{max} 224 (7600, 95% ETHANOL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2 H), 7.10 (d, J = 8 Hz, 2 H), 2.74 (t, J = 7 Hz, 2 H), 2.60 (t, J = 8 Hz, 2 H), 2.25 (s, 2 H), 1.64 (m, 2 H), 1.49 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 141.2, 131.8, 130.1, 128.8, 42.3, 35.4, 33.6, 29.0; IR (liq.) 3365 (b), 3296 (b), 3026, 2933 (s), 2858 (s), 2170 (w), 1996 (w), 1576, 1492 (s), 1460, 1093 (s), 1016 (s), 831, 821, 804, cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{14}ClN + H_1$ 184.0893, found 184.0879.

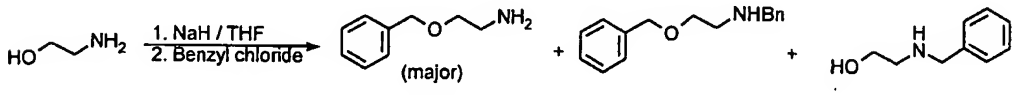
4-(p-methoxyphenyl)butanamide (35b)

A mixture of 4-(p-methoxyphenyl)butyric acid (**34b**) (6.50 g, 33.5 mmol) and thionyl chloride (10.0 mL, 137 mmol) in 50 mL $CHCl_3$ was stirred at reflux for 5.5 h. Solvent and excess thionyl chloride were removed *in vacuo*, and residue was twice diluted with 25 mL toluene and evaporated to remove traces of thionyl chloride. To a solution of the residue in 10 mL toluene was added slowly 30 mL of cold concentrated NH_4OH. The precipitate was filtered off and recrystallized in $CHCl_3$/heptane to give **35b** (3.68 g, 57%) as a white solid. UV λ_{max} 223 (10200, 95% EtOH); ^{1}H NMR (400 MHz, CDCl3) δ 7.10 (d, J = 9 Hz, 2 H), 6.84 (d, J = 9 Hz, 2 H), 5.44 (s, 2 H), 3.80 (s, 3 H), 2.63 (t, J = 7 Hz, 2 H), 2.23 (d, J = 8 Hz, 2 H), 1.96 (m, 2 H); 13C NMR (CDCl3) δ 175.5, 158.3, 133.8, 129.7, 114.2, 55.6, 35.4, 34.5, 27.4; IR (drift) 3366 (s), 2479 (w), 2355 (w), 2285 (w), 2053 (w), 1993 (w), 1656 (s), 1628 (s), 1512 (s), 1416 (s), 1304 (s), 1243 (s), 1230 (s), 1031 (s), 838 (s), cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.42; H, 8.03; N, 7.24.

4-(p-methoxyphenyl)butylamine (36b) (Ali, F.E.; Dandridge, P.A.; Gleason, J.G.; Krell, R.D.; Kruse, C.H.; Lavanchy, P.G; Snader, K.M. *J. Med. Chem.*, **1982**, *25*, 947)

To a stirred suspension of lithium aluminum hydride (4.40 g, 116 mmol) in 120 mL diethyl ether was added dropwise a solution of **35b** (5.60 g, 29.0 mmol) in 10 mL THF, and

stirred at rt for 1 h. To the reaction mixture was added 7.5 mL water, 7.5 mL 5 N NaOH(aq), and 20 mL water. The organics were removed from the emulsion which was dissolved in water and extracted with ether. The organic portions were dried over Na_2SO_4(s), and condensed to give **36b** (5.10 g, 98%) as an oil. UV λ_{max} 223 (9410, 95% EtOH). (400 MHz, $CDCl_3$) δ 7.10 (d, J = 9 Hz, 2 H), 6.83 (d, J = 9 Hz, 2 H), 3.79 (s, 3 H), 2.71 (t, J = 7 Hz, 2 H), 2.58 (t, J = 7 Hz, 2 H), 1.63 (m, 2 H), 1.48 (m, 2 H); IR (liq.) 2933 (s), 2856, 2145 (w), 2059 (w), 1996 (w), 1612 (s), 1584, 1513 (s), 1461, 1442, 1246 (s), 1178, 1034 (s), 827, 822, cm^{-1} HRMS (FAB) calcd for $C_{11}H_{17}NO + H_1$ 180.1388, found 180.1387.



37 38 39 40

2-(benzyloxy)ethylamine (38) (Hu, X.E.; Cassady, J.M. *Synthetic Comm.*, 1995, *25*, 907)

To a solution of distilled ethanolamine (**37**) (1.81mL, 30.0 mmol) in 30 mL of dry THF, was added NaH (1.2 g 30.0 mmol) as a 60% dispersion in mineral oil, in small portions at rt. The mixture was stirred at reflux for 30 min., benzyl chloride (2.88 mL, 25.0 mmol) was added, and stirred at reflux for an additional 4.5 h. The mixture was cooled to rt, 10 mL water was added, and solvent evaporated *in vacuo*. The residue was partitioned between 1 N HCl(aq) and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 to remove side product **39**. The aqueous portion was adjusted to pH 13 with 10% NaOH(aq) and extracted with CH_2Cl_2. The extracts were condensed and purified by flash chromatography (10% MeOH (saturated with NH_3)/CH_2Cl_2) to give **38** (0.24 g, 10%) as a yellow oil. R_f(10% MeOH(saturated with NH_3)/CH_2Cl_2) = 0.47; UV λ_{max} 251 (162, 95% ETHANOL); 1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.55 (s, 2 H), 3.53 (t, J = 5 Hz, 2 H), 2.90 (t, J = 5, 2 H), 1.68 (s, 2 H); ^{13}C NMR (CDCl3) δ 138.7, 128.8, 128.1, 128.0, 73.5, 72.9, 42.3; IR (liq.) 3371, 3302 (b), 3030, 2924 (b), 2860 (s), 2202 (w), 1955 (w), 1496, 1453 (s), 1356, 1101 (s), 1069, 1028, 739 (s), 698 (s), cm^{-1}. HRMS (FAB) calcd for $C_9H_{13}NO + H_1$ 152.1075, found 152.1074.

Library Synthesis

The production of this library required seven steps using solid support. Three steps were carried out in a 96 well format. The AMEBA (acid sensitive methoxy benzaldehyde) linker was

prepared by reacting Merrifield resin and 4-hydroxy-2-methoxybenzaldehyde with sodium methoxide (see Scheme I). The AMEBA resin was then treated with the corresponding amine and $NaBH(OAc)_3$ to give the corresponding reductive amination product. The tyrosine scaffold (5) was then coupled to the various amine resins using DIC and HOBT in DMF. The Fmoc protecting group was then removed with piperidine/ DMF (1:1). The resin was then plated in a 96 well Robbins block then coupled to the corresponding acid with DIC and HOBT in DMF. The diethyl ester was hydrolyzed with excess LiOH in THF: MeOH (1:1) for 5-14 h at rt to yield the dicarboxylic acid on resin. The use of THF : MeOH (1:1) is crucial for this hydrolysis. The use of excess LiOH and neat MeOH, THF and DMF failed to yield the diacid. The product was then cleaved from the resin with 20% TFA / CH_2Cl_2 solution. The resin was cleaved twice to yield the maximum possible product. The second cleavage resulted in approximately 10-20% more product without any change in purity levels.

Step 1: Preparation of AMEBA Linker A suspension of Merrifield resin (2.10g, 3.47 mmol) in 50 mL of DMF was treated with solid sodium methoxide (560 mg, 10.4 mmol). To the solution was added 4-hydroxy-2-methoxybenzaldehyde (1.58 g, 10.4 mmol). The reaction mixture was heated to 60-70°C for 24 h. The resin was then washed with DMF, MeOH, water, MeOH, CH_2Cl_2, and MeOH (3x 10 mL). IR indicated strong absorption at 1681 cm^{-1}.

Step 2: Reductive Amination A suspension of AMEBA (1.04g 1.12 mmol) in 25 mL of $C_2H_4Cl_2$ was treated with phenylbutyl amine (0.36 mL, 2.3 mmol) and $NaBH(OAc)_3$ (479 mg, 2.26 mmol). The reaction mixture was stirred at rt for 3 h. The resin was then washed with CH_2Cl_2, DMF, MeOH and CH_2Cl_2 (3x 10 mL). IR indicated disappearance of strong absorption at 1681 cm^{-1}.

Step 3: Coupling Resin to Intermediate 5 A suspension of resin (734 mg, 0.751 mmol) in 20 mL of DMF was treated with tyrosine scaffold **5** (632 mg, 1.13 mmol), hydroxybenzotriazole (HOBT) (24 mg, 0.18 mmol), diisopropyl carbodiimide (DIC) (175 μL, 1.12 mmol). The reaction mixture was stirred at rt for 2 h. The resin was tested for the presence of any secondary amine using the choranil test. A sample of resin 1-5 mg was mixed with one drop of 2% acetaldehyde in DMF and one drop of 2% chloranil in DMF. After 5 min the resin showed no color change; a control containing a secondary amine stained blue (Rzeszotarska, B.; Nadolska,

B.; Tarnawski, J. *Liebigs Ann. Chem.* 1981, *7*, 1294). The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 10 mL).

Step 4: Fmoc Removal Resin (1.14 g, 0.751 mmol) was suspended in 10 mL of piperidine/ DMF (1:5) and stirred for 30 min. at rt. The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 10 mL).

Step 5: Coupling Resin to Acid The resin was plated in a 96 well Robbins block (approx. 35 mg, 0.027 mmol). To each well was added as a slurry of DMF/ CH_2Cl_2 and the resin was dried. Standard solutions of acid (1.26 mmol) in 7.5 mL of DMF, HOBT (119 mg, 0.88 mmol) in 20mL of DMF and DIC (1.3 mL, 8.4 mmol) in 20 mL DMF were prepared. To the resin in each well was added the standard acid solution (0.50 mL, 0.084 mmol), DIC (0.20 mL DMF, 0.084 mmol) and HOBT (0.20 mL DMF, 0.009 mmol). The Robbins plate was then rotated for 5 h. The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 1 mL).

Step 6: Hydrolysis of Esters A standard solution of LiOH (2.26 g, 53.9 mmol) in 25 mL of MeOH and 25 mL of THF was prepared. The resin (approx. 35 mg, 0.027 mmol) in each well was treated with 0.5 mL of standard LiOH solution (0.62 mmol). The Robbins plate was rotated for 14 h. The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 1 mL).

Step 7: Cleavage The resin (approx. 35 mg, 0.027 mmol) in each well was treated with 0.50 mL of TFA/ CH_2Cl_2 (1:5). The robbins block was rotated for 30 min. The resin was washed with CH_2Cl_2 (3x 0.2 mL) and the filtrate collected. This process was repeated to insure all the product was cleaved from the resin.

Purification

The entire library was purified by reverse phase HPLC. The average purity after purification of the eleven samples was >99%. All samples tested indicated a purity >98% by analytical HPLC. The average yield after purification was 17% (2-3 mg per well on average). The preparative HPLC system used a Gilson 215 liquid robotics autosampler/fraction collector. The chromatography utilized a three-pump system of Rainin pump heads equipped with 10 mL/min or 50 mL/min pump solvent delivery heads and a Gilson solvent mixing chamber. Two pumps were used for solvent delivery, and one was used for flushing the system at the

completion of the series of chromatography runs. UV absorbance was monitored using a Knauer variable wavelength UV detector equipped with a 10 mm path length analytical flow cell. The entire system was controlled by Gilson Unipoint software v. 1.65 which was used for data acquisition and analysis.

Samples were prepared for injection by dissolving each in 1-2 mL MeOH and housing them in 96 deep-well microtiter plates (2 mL/well). Injections for the chromatography loaded the entire sample into a 2.0 mL injection loop installed on the Gilson 819/Rheodyne Injector Module.

The HPLC method used in this study is as follows:

Column:	YMC GuardPack C8 (20 X 50 mm, 5 μ, 120 A)
Mobile A:	water + 0.05% trifluoroacetic acid (TFA)
Mobile B:	acetonitrile
Flow Rate.	10 mL/ min
Gradient:	10% B 0-2 min, 10-100% B 2-23 min, 100% B 23-25 min, re-equilibrate for 3 min
Detection:	UV absorbance at 220 nm, Knauer UV detector with 10 mm flow cell
Fraction Collection:	Gilson 215, 15% AUFS threshold, 9 mL maximum/tube in 13 X 100 mm disposable tubes

Mass Spectrometry

The entire library was analyzed by mass spectrometry after reverse phase HPLC. All of the 64 recovered compounds were positively identified by a molecular ion peak.

Library Compounds (Examples 9-1 to 9-64)

Table A

Ex. No.	Compound Name	Mol. Wt.	Mass DATA (M+)	Post Purification HPLC Analysis	Retention Time (min)	1H NMR
9-1	2-(carboxymethoxy)-5-[(2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid	491.93	493.1			Y
9-2	2-(carboxymethoxy)-5-[(2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid	526.38	544 (M + NH3)+			Y
9-3	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(pentylamino)-2-[(2-pyrazinylcarbonyl)amino]propyl}benzoic acid	458.48	459.1			Y
9-4	2-(carboxymethoxy)-5-[(2S)-2-(3-furoylamino)-3-oxo-3-(pentylamino)propyl]benzoic acid	446.46	447.2			Y
9-5	2-(carboxymethoxy)-5-[(2S)-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid	525.56	526.1	>98%	3.67	
9-6	5-[(2S)-2-{[(2S)-2-(acetylamino)-3-phenylpropanoyl]amino}-3-oxo-3-(pentylamino)propyl]-2-(carboxymethoxy)benzoic acid	541.61	542.2			
9-7	2-(carboxymethoxy)-5-{(2S)-2-[(cycloheptylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	538.65	539.2			
9-8	5-{(2S)-2-(benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	518.57	519.2			

9-9	2-(carboxymethoxy)-5-{(2S)-2-[(4-chlorobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	553.02	554.1	>98%	4.71	
9-10	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}benzoic acid	590.53	591.0			
9-11	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid	519.56	520.2			
9-12	2-(carboxymethoxy)-5-{(2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	554	555.1			
9-13	2-(carboxymethoxy)-5-{(2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	588.45	589.9			
9-14	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(2-pyrazinylcarbonyl)amino]propyl}benzoic acid	520.55	521.1			
9-15	2-(carboxymethoxy)-5-{(2S)-2-(3-furoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	508.53	509.1	>98%	4.29	
9-16	2-(carboxymethoxy)-5-{(2S)-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	587.64	588.1			

9-17	5-{(2S)-2-{[(2S)-2-(acetylamino)-3-phenylpropanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	603.68	604.1			
9-18	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-[(cycloheptylcarbonyl)amino]-3-oxopropyl}benzoic acid	573.09	574.1			
9-19	5-((2S)-2-(benzoylamino)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	553.02	554.2			
9-20	2-(carboxymethoxy)-5-((2S)-2-[(4-chlorobenzoyl)amino]-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)benzoic acid	587.46	589.0			
9-21	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}benzoic acid	624.98	626.2	>98%	3.99	
9-22	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid	554	555.1			
9-23	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-oxopropyl)benzoic acid	588.45	589.1			

9-24	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxopropyl)benzoic acid	622.89	623.9			
9-25	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-[(2-pyrazinylcarbonyl)amino]propyl}benzoic acid	554.99	556.1	>98%	4.43	
9-26	2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-(3-furoylamino)-3-oxopropyl]benzoic acid	542.98	544.1			
9-27	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-oxopropyl)benzoic acid	622.08	623.1			
9-28	5-((2S)-2-{[(2S)-2-(acetylamino)-3-phenylpropanoyl]amino}-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	638.12	639.2			
9-29	2-(carboxymethoxy)-5-((2S)-2-[(cycloheptylcarbonyl)amino]-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	568.67	569.1			
9-30	5-((2S)-2-(benzoylamino)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	548.6	549.1			
9-31	2-(carboxymethoxy)-5-((2S)-2-[(4-chlorobenzoyl)amino]-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	583.04	584.3			

9-32	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}benzoic acid	620.56	621.0			
9-33	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid	549.59	550.1	>98%	3.83	
9-34	2-(carboxymethoxy)-5-((2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	584.03	585.2			
9-35	2-(carboxymethoxy)-5-((2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	618.48	619.9	>98%	4.59	
9-36	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-[(2-pyrazinylcarbonyl)amino]propyl}benzoic acid	550.57	551.1			
9-37	2-(carboxymethoxy)-5-((2S)-2-(3-furoylamino)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	538.56	539.1			
9-38	2-(carboxymethoxy)-5-((2S)-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid	617.66	618.1			

9-39	5-((2S)-2-{[(2S)-2-(acetylamino)-3-phenylpropanoyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	633.7	634.1			
9-40	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-2-[(cycloheptylcarbonyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid	540.62	541.2			
9-41	5-((2S)-2-(benzoylamino)-3-{[2-(benzyloxy)ethyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	520.54	521.1			
9-42	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-2-[(4-chlorobenzoyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid	554.99	556.0			
9-43	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	592.51	593.0			
9-44	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-[(3-pyridinylcarbonyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	521.53	522.1			
9-45	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	555.98	557.1	>98%	3.83	
9-46	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	590.42	592.0			
9-47	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-[(2-pyrazinylcarbonyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	522.52	523.1			

9-48	5-[(2S)-3-{[2-(benzyloxy)ethyl]amino}-2-(3-furoylamino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid	510.51	511.1			
9-49	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	589.61	590.0			
9-50	5-((2S)-2-{[(2S)-2-(acetylamino)-3-phenylpropanoyl]amino}-3-{[2-(benzyloxy)ethyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	605.65	606.0			
9-51	5-[(2S)-2-(benzoylamino)-3-oxo-3-(propylamino)propyl]-2-(carboxymethoxy)benzoic acid	428.45	429.2			
9-52	2-(carboxymethoxy)-5-[(2S)-2-[(4-chlorobenzoyl)amino]-3-oxo-3-(propylamino)propyl]benzoic acid	462.89	463.1			
9-53	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(propylamino)-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}benzoic acid	500.41	501.1			
9-54	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(propylamino)-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid	429.43	430.2			
9-55	2-(carboxymethoxy)-5-[(2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(propylamino)propyl]benzoic acid	463.88	464.1			
9-56	2-(carboxymethoxy)-5-[(2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(propylamino)propyl]benzoic acid	498.32	516 (M + NH3)+			

9-57	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(propylamino)-2-[(2-pyrazinylcarbonyl)amino]propyl}benzoic acid	430.42	431.2			
9-58	2-(carboxymethoxy)-5-[(2S)-2-(3-furoylamino)-3-oxo-3-(propylamino)propyl]benzoic acid	418.41	419.1			
9-59	2-(carboxymethoxy)-5-[(2S)-2-{[(5-methoxy-1H-indol-2-yl)carbonyl]amino}-3-oxo-3-(propylamino)propyl]benzoic acid	497.51	498.1			
9-60	2-(carboxymethoxy)-5-[(2S)-2-[(cycloheptylcarbonyl)amino]-3-oxo-3-(pentylamino)propyl]benzoic acid	476.57	477.2			
9-61	5-[(2S)-2-(benzoylamino)-3-oxo-3-(pentylamino)propyl]-2-(carboxymethoxy)benzoic acid	456.5	457.2	>98%	3.77	
9-62	2-(carboxymethoxy)-5-[(2S)-2-[(4-chlorobenzoyl)amino]-3-oxo-3-(pentylamino)propyl]benzoic acid	490.94	491.1			Y
9-63	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(pentylamino)-2-[(2,3,5,6-tetrafluorobenzoyl)amino]propyl}benzoic acid	528.46	529.1			
9-64	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-(pentylamino)-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid	457.49	458.2			Y

The following NMR data were determined

Ex. 9-64; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (d, J = 5 Hz, 1 H), 8.77 (d, J = 3 Hz, 2 H), 8.12 (t, J = 2 Hz, 1 H), 7.81 (m, 2 H), 7.40 (dd, J = 2, 6 Hz, 1 H), 6.89 (d, J = 6 Hz, 1 H), 4. 6 9 (s, 2 H), 4.62 (m, 1 H), 3.07 (m, 3 H), 2.94 (m, 1 H), 1.40 (m, 2 H), 1.26 (m, 4 H), .85 (J = 5 Hz, 3H).

Ex-9-3; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.10 (s, 1 H), 8.87 (d, J = 2 Hz, 1 H), 8.72 (m, 1 H), 8.65 (d, J = 6 Hz, 1 H), 8.15 (m, 1 H), 7.53 (d, J = 2 Hz, 1 H), 7.30 (dd, J = 2, 6 Hz, 1 H), 6.87 (d, J = 6 Hz, 1 H), 4.69 (s, 2 H), 4.65 (m, 1 H), 3.06 (m, 4 H), 1.38 (m, 2 H), 12.3 (m, 4 H), 0.84 (t, J = 6 Hz, 3 H).

Ex. 9-62; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (d, J = 6 Hz, 1 H), 8.05 (m, 1 H), 7.80 (d, J = 9 Hz, 2 H), 7.66 (d, J = 2 Hz, 1 H), 7.49 (d, J = 8 Hz, 2 H), 7.41 (dd, J = 2, 6 Hz, 1 H), 6.88 (d, J = 6 Hz, 1 H), 4.68 (s, 2 H), 4.58 (m, 1 H), 3.00 (m, 4 H), 1.38 (m, 2 H), 1.23 (m, 4 H), 0.83 (t, J = 6 Hz, 3 H).

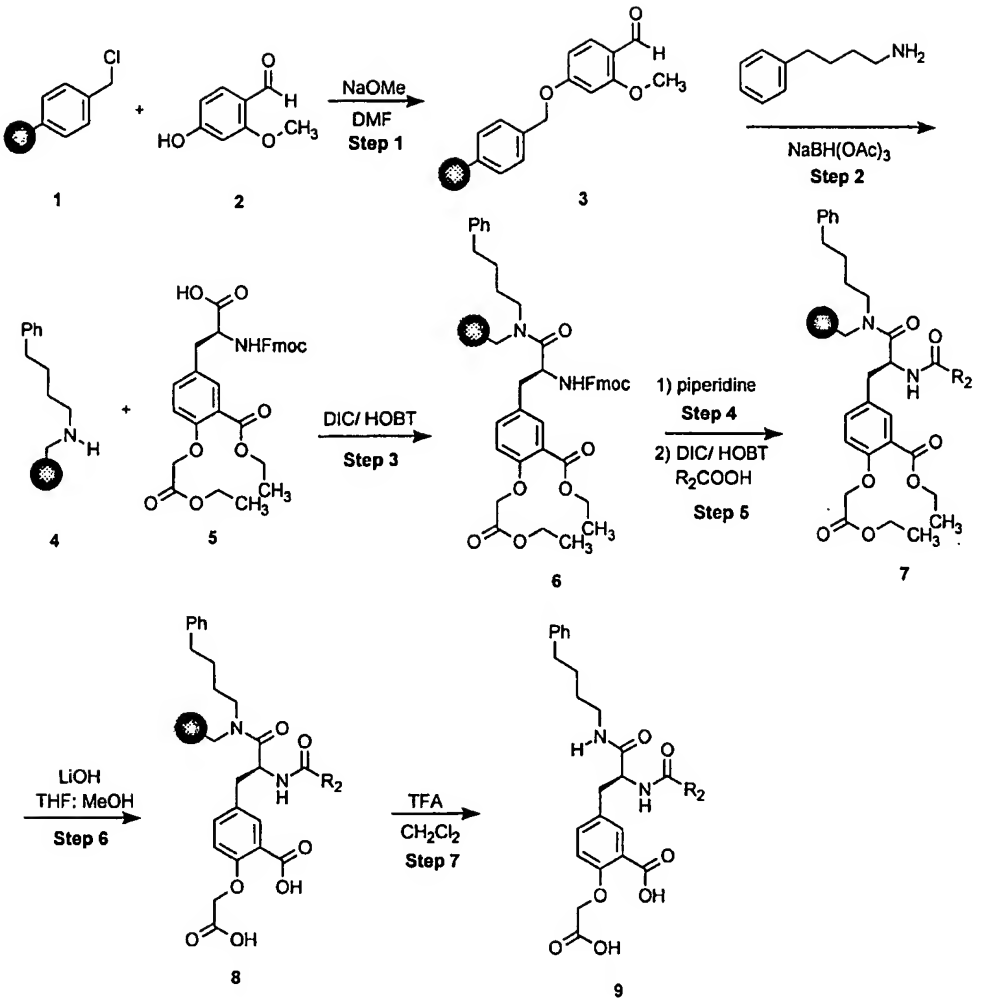
Ex. 9-1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, J = 6 Hz, 1 H), 8.73 (d, J = 2 Hz, 1 H), 8.16 (dd, J = 3, 6 Hz, 1 H), 8.10 (m, 1 H), 7.66 (s, 1 H), 7.59 (d, J = 8 Hz, 1 H), 7.39 (dd, J = 2, 7 Hz, 1 H), 6.88 (d, J = 9 Hz, 1 H), 4.68 (s, 2 H), 4.58 (m, 1 H), 2.90 (m, 4 H), 1.37 (m, 2 H), 1.23 (m, 4 H), 0.83 (t, J = 5 Hz, 3 H)

Ex. 9-2; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (d, J = 6 Hz, 1 H), 8.53 (s, 1 H), 8.26 (s, 1 H), 8.07 (m, 1 H), 7.68 (s, 1 H), 7.40 (m, 1 H), 6.90 (d, J = 6 Hz, 1 H), 4.70 (s, 2 H), 4.58 (m, 1 H), 3.03 (m, 2 H), 2.89 (m, 1 H), 1.38 (m, 1 H), 1.25 (m, 4 H), 0.84 (t, J = 6 Hz, 3H).

Ex. 9-4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, J = 10 Hz, 1 H), 8.16 (s, 1 H), 8.03 (m, 1 H), 7.67 (m, 2 H), 7.39 (m, 1 H), 6.89 (d, J = 10 Hz, 1 H), 6.83 (s, 1 H), 4.70 (s, 2 H), 4.56 (m, 1 H), 3.03 (m, 2 H), 2.96 (m, 1 H), 2.85 (m, 1 H), 1.37 (m, 2 H), 1.23 (m, 4 H), 0.84 (t, 3 H).^{1}H NMR.

EXAMPLE 10: One-dimensional library of 5-substituted-2-carbomethoxybenzoic acids

Scheme 3



Chemistry Summary

The combination solid-phase/solution-phase synthetic sequence was designed to prepare an 88-member one-dimensional library of 5-substituted-2-carboxymethoxybenzoic acids in a 96-well format as illustrated in Scheme 3. The synthesis was based on the use of the AMEBA linker (acid sensitive **m**ethoxy**b**enzal**d**ehyde, **3**) , selected due to its ease of cleavage and versatility in the reductive amination step, and the intermediate **5**, synthesized in a seven step sequence as described below. The key resin **3** was synthesized by treating Merrifield resin with 2-methoxy-4-hydroxybenzaldehyde according to the literature procedure (Fivush, A.M.; Willson, T.M. *Tetrahedron Lett.* **1997**, *38*, 7151. Sarantakis, D.; Bicksler, J.J. *Tetrahedron Lett.*, **1997**, *38*, 7325e). The functionalized resin **3** was treated with 4-phenylbutyl amine and sodium triacetoxyborohydride to provide resin **4**. Attachment of the scaffold **5** to the resin was performed utilizing the standard conditions of DIC/HOBt in DMF. A deprotection/

condensation protocol was followed to attach the diversity element to give 7. Hydrolysis of the diester was then followed by removal of the products from the resin with 20% TFA/CH_2Cl_2.

Intermediate Synthesis

Scaffold 5 (see Scheme 3 above), (2S)-3-[3-ethyoxycarbonyl)-4-(2-ethoxy-2-oxoethoxy)phenyl]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propanoic acid, was prepared as described in Example 9 above.

Diversity Elements

Compound Name
benzoic acid
diethylphosphonoacetic acid
pentafluoropropionic acid
S-benzylthioglycolic acid
2-methyl-6-nitrobenzoic acid
2-formylphenoxyacetic acid
4-cyanocinnamic acid
benzoylformic acid
1-phenyl-1-cyclopentylcarboxylic acid
2-cyanobenzoic acid
4-oxo-2-thioxo-3-thiazolidineacetic acid
pivalic acid
p-chlorophenylpropiolic acid
2-benzoylbenzoic acid
3,4-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylic acid
isonicotinic acid
cyclopropanecarboxylic acid
3-cyclopentylpropionic acid
1-methyl-1-cyclohexanecarboxylic acid
2,5-dimethoxybenzoic acid
2-biphenylcarboxylic acid
2-acetylbenzoic acid
o-toluic acid

3-fluorobenzoic acid

3,4-dichlorobenzoic acid

m-anisic acid

3,4-dimethoxybenzoic acid

3,4,5-trimethoxybenzoic acid

3,5-dimethoxybenzoic acid

4-bromobenzoic acid

4-chloro-*o*-anisic acid

4-dimethylaminobenzoic acid

4-(trifluoromethoxy)benzoic acid

4-butoxybenzoic acid

4-biphenylcarboxylic acid

4-acetylbenzoic acid

α,α,α-trifluoro-*p*-toluic acid

4-tert-butylbenzoic acid

p-toluic acid

3-methoxy-4-methylbenzoic acid

hydrocinnamic acid

3-(4-methoxyphenyl)propionic acid

3-benzoylpropionic acid

1-methylpyrrole-2-carboxylic acid

5-bromo-2-furoic acid

2-naphthoic acid

(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid

(*R*)-(-)-α-methoxyphenylacetic acid

4-fluorophenoxyacetic acid

phenylacetic acid

2-chlorophenylacetic acid

2-methoxyphenylacetic acid

o-tolylacetic acid

3-chlorophenylacetic acid

m-methoxyphenylacetic acid

(α,α,α-trifluoro-*m*-tolyl)acetic acid

p-chlorophenylacetic acid

4-methoxyphenylacetic acid

(α,α,α-trifluoro-*p*-tolyl)acetic acid

4-phenylbutyric acid

4-(4-methoxyphenyl)butyric acid

4-benzoylbutyric acid

5-phenylvaleric acid

undecylenic acid

3-methyl-2-thiophenecarboxylic acid

4-(2-thienyl)butyric acid

3-thiophenecarboxylic acid

1-methylindole-2-carboxylic acid

piperonylic acid

picolinic acid

3-quinolinecarboxylic acid

coumarin-3-carboxylic acid

4-(methylsulfonyl)benzoic acid

2-methoxy-4-(methylthio)benzoic acid

(2-pyrimidylthio)acetic acid

2-fluoro-4-(trifluoromethyl)benzoic acid

3-pyridylacetic acid hydrochloride

2-methylnicotinic acid

2,3,5,6-tetramethyl-benzoic acid

β-(*p*-chlorophenyl)propionic acid

(3,5-dimethoxyphenyl)acetic acid

3-(3,4-methylenedioxyphenyl)propionic acid

6-methylpicolinic acid

1-acetylpiperidine-4-carboxylic acid

4-cyclohexylbenzoic acid

5-chloro-2-thiophenecarboxylic acid

3-methylindene-2-carboxylic acid

8-quinolinecarboxylic acid

3,5-dimethylisoxazole-4-carboxylic acid

2,4-dimethylthiazole-5-carboxylic acid

3-(4-fluorophenyl)propionic acid

7-chlorobenzofuran-2-carboxylic acid

(*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid

(±)-camphorcarboxylic acid

pinonic acid

1-adamantanecarboxylic acid

tetrahydro-3-furoic acid

3-fluoro-2-methyl-benzoic acid

2,6-dimethoxynicotinic acid

1,4-benzodioxan-2-carboxylic acid

2-fluoro-5-methylbenzoic acid

2-norbornaneacetic acid

2-phenoxypropionic acid

anti-3-oxotricyclo(2.2.1.02,6)heptane-7-carboxylic acid

Library Synthesis

The production of the library required seven steps using solid support. Three steps were carried out in a 96 well format. The AMEBA (acid sensitive methoxy benzaldehyde) linker was prepared by reacting Merrifield resin and 4-hydroxy-2-methoxybenzaldehyde with sodium methoxide (see Scheme 3). The AMEBA resin was then treated with 4-phenylbutyl amine and $NaBH(OAc)_3$ to give the corresponding reductive amination product. The tyrosine scaffold (**5**) was then coupled to this amine resin using DIC and HOBT in DMF. The Fmoc protecting group was then removed with piperidine/ DMF (1:1). The resin was then plated in a 96 well Robbins block and coupled to the corresponding acid with DIC and HOBT in DMF. After thorough washing, the resin was subjected to the coupling conditions a second time. The diethyl ester was hydrolyzed with excess LiOH in THF: MeOH (1:1) for 5-14 h at rt to yield the dicarboxylic acid on resin. The product was then cleaved from the resin with 20% TFA / CH_2Cl_2 solution. The resin was cleaved twice to yield the maximum possible product. The second cleavage resulted in approximately 10-20% more product without any change in purity levels.

Step 1: Preparation of AMEBA Linker A suspension of Merrifield resin (10.3g, 12.9 mmol) in 200 mL of DMF was treated with solid sodium methoxide (2.08 g, 38.5 mmol) and 4-hydroxy-2-methoxybenzaldehyde (5.81 g, 38.2 mmol). The reaction mixture was heated to 60°C for 24 h. The resin was then washed with DMF, MeOH, water, MeOH, CH_2Cl_2, and MeOH (3x 50 mL), and dried to a constant weight (9.31 g) under high vacuum. IR indicated strong absorption at 1681 cm^{-1}.

Step 2: Reductive Amination A suspension of AMEBA (0.804 g 0.878 mmol) in 25 mL of 1,2-dichloroethane was treated with 4-phenylbutyl amine (0.29 mL, 1.8 mmol) and $NaBH(OAc)_3$ (394 mg, 1.86 mmol). After stirring at room temperature for 4h, the resin was washed with CH_2Cl_2, DMF, MeOH and CH_2Cl_2 (3x each) and dried under high vacuum to a constant mass (0.807g). IR indicated disappearance of strong absorption at 1681 cm^{-1}.

Step 3: Coupling Resin to Intermediate 5 A suspension of resin (0.724 g, 0.689 mmol) in 20 mL of DMF was treated with tyrosine scaffold **5** (0.584 g, 1.04 mmol), hydroxybenzotriazole (HOBt) (32 mg, 0.24 mmol), diisopropyl carbodiimide (DIC) (0.13 mL, 0.24 mmol). The reaction mixture was stirred at rt for 2.5 h. The resin was tested for the presence of any secondary amine using the choranil test (a sample of resin 1-5 mg was mixed with one drop of 2% acetaldehyde in DMF and one drop of 2% chloranil in DMF). After 5 min the resin showed no color change; a control containing a secondary amine stained blue (Vojkovsky T. *Peptide Research* **1995**, 4, 236). The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x each) and dried under high vacuum to constant mass (0.857 g).

Step 4: Fmoc Removal Resin (0.855 g, 0.0.537 mmol) was suspended in 10 mL of piperidine/ DMF (1:5) and stirred for 45 min. at rt. The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 10 mL) and dried under high vacuum to constant mass (0.528 g).

Step 5: Coupling Resin to Acid The resin was plated into a 96 well Robbins block (approx. 60 mg, 0.045 mmol/well) as a suspension in DMF/ CH_2Cl_2 and dried. Standard solutions of acid (0.50 mL of a 0.27M stock in DMF), HOBt (200 μL of a 0.0675M stock in DMF) and DIC (200μL of a 0.675M stock in DMF) were added to each well. The Robbins block was then rotated for 18 h at ambient temperature. The resin was washed with DMF, CH_2Cl_2, MeOH, CH-

$_2Cl_2$ (3x each). The coupling was repeated by adding the same amounts of reagents as above, rotating for an additional 18h, and washing as above.

Step 6: Hydrolysis of Esters A standard solution of 0.90M LiOH in 1:1 MeOH/THF was prepared. The resin (approx. 60 mg, 0.045 mmol) in each well was treated with 1.0 mL of standard LiOH solution (0.90 mmol). The Robbins plate was rotated for 6h, and the resin was washed with MeOH/CH_2Cl_2 (3x).

Step 7: Cleavage The resin (approx. 60 mg, 0.045 mmol) in each well was treated with 0.50 mL of TFA/ CH_2Cl_2 (1:5). The Robbins block was rotated for 30 min. The resin was washed with CH_2Cl_2 (3x 0.2 mL) and the filtrate collected. This process was repeated to ensure complete cleavage from the resin.

Purification

The entire library from the first cleavage iteration was purified by reverse phase HPLC. Based on HPLC analysis of 54 randomly chosen samples, the average purity of these compounds was 98%. The average yield after purification was 3% (0.6 mg per well on average). The recovered weight of each compound was determined by transferring the appropriate fraction(s) to a tared vial and removing the solvent in a Savant concentrator.

The preparative HPLC system used a Gilson 215 liquid robotics autosampler/fraction collector. The chromatography utilized a three-pump system of Rainin pump heads equipped with 10 mL/min or 50 mL/min pump solvent delivery heads and a Gilson solvent mixing chamber. Two pumps were used for solvent delivery, and one was used for flushing the system at the completion of the series of chromatography runs. UV absorbance was monitored using a Knauer variable wavelength UV detector equipped with a 10 mm path length analytical flow cell. The entire system was controlled by Gilson Unipoint software v. 1.65 which was used for data acquisition and analysis.

Samples were prepared for injection by dissolving each in 1-2 mL MeOH and housing them in 96 deep-well microtiter plates (2 mL/well). No filtering was performed on those samples. Injections for the chromatography loaded the entire sample into a 2.0 mL injection loop installed on the Gilson 819/Rheodyne Injector Module.

The HPLC method used in this study is as follows:

Column:	YMC GuardPack C8 (20 X 50 mm, 5 μ, 120 A)
Mobile A:	water + 0.05% trifluoroacetic acid (TFA)
Mobile B:	acetonitrile
Flow Rate.	10 mL/ min
Gradient:	10% B 0-2 min, 10-100% B 2-23 min, 100% B 23-25 min, re-equilibrate for 3 min
Detection:	UV absorbance at 220 nm, Knauer UV detector with 10 mm flow cell
Fraction Collection:	Gilson 215, 15% AUFS threshold, 9 mL maximum/tube in 13 X 100 mm disposable tubes

Mass Spectrometry

The entire library was analyzed by mass spectrometry after reverse phase HPLC. All but five of the 85 recovered compounds were positively identified by a molecular ion peak.

Library Compounds (Examples 10-1 to 10-80)

The following compounds were obtained in the library.

Table B

Ex. No.	Compound Name	M.W.	Observed Molecular ion (ES-)	Amount of compound (g) (after HPLC)	Purity by HPLC (220nm)	Ret. Time (min.)
10-1	2-(carboxymethoxy)-5-{(2S)-2-[(3-cyclopentylpropanoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	538.64	537.3	0.0010		
10-2	2-(carboxymethoxy)-5-{(2S)-2-[[(1-methylcyclohexyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	538.64	537.3	0.0012	99	7.06
10-3	2-(carboxymethoxy)-5-{(2S)-2-[(2,5-dimethoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	578.62	577.2	0.0013	99	6.52
10-4	5-{(2S)-2-[([1,1'-biphenyl]-2-ylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	594.67	593.3	0.0022	99	7.32
10-5	2-(carboxymethoxy)-5-{(2S)-2-[(2-methylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	532.60	531.2	0.0008		
10-6	2-(carboxymethoxy)-5-{(2S)-2-[(3-fluorobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	536.56	535.1	0.0006	99	6.48
10-7	2-(carboxymethoxy)-5-{(2S)-2-[(3,4-dichlorobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	587.46	585.0	0.0019	99	7.61
10-8	2-(carboxymethoxy)-5-{(2S)-2-[(3-methoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	548.59	547.2	0.0015	99	6.38
10-9	2-(carboxymethoxy)-5-{(2S)-2-[(3,4-dimethoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	578.62	577.0	0.0008	97.3	5.91

10-10	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3,4,5-trimethoxybenzoyl)amino]propyl}benzoic acid	608.65	607.2	0.0004	99	6.21
10-11	2-(carboxymethoxy)-5-{(2S)-2-[(3,5-dimethoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	578.62	576.9	0.0001	99	6.67
10-12	5-{(2S)-2-[(4-bromobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	597.47	596.8	0.0008	99	7.13
10-13	2-(carboxymethoxy)-5-{(2S)-2-[(4-chloro-2-methoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	583.04	581.0	0.0011	99	7.18
10-14	2-(carboxymethoxy)-5-{(2S)-2-{[4-(dimethylamino)benzoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	561.64	560.0	0.0004	99	6.54
10-15	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[4-(trifluoromethoxy)benzoyl]amino}propyl)benzoic acid	602.57	600.9	0.0003	99	7.62
10-16	5-{(2S)-2-[(4-butoxybenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	590.68	589.2	0.0008	99	8.07
10-17	5-{(2S)-2-[([1,1'-biphenyl]-4-ylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	594.67	539.0	0.0005	99	7.96
10-18	5-{(2S)-2-[(4-acetylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	560.61	559.1	0.0005	99	5.99
10-19	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[4-(trifluoromethyl)benzoyl]amino}propyl)benzoic acid	586.57	585.0	0.0002		

10-20	5-{(2S)-2-{[4-(tert-butyl)benzoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	574.68	573.1	0.0015		
10-21	2-(carboxymethoxy)-5-{(2S)-2-[(4-methylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	532.60	531.1	0.0010		
10-22	2-(carboxymethoxy)-5-{(2S)-2-[(3-methoxy-4-methylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	562.62	561.0	0.0005	99	7.01
10-23	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-phenylpropanoyl)amino]propyl}benzoic acid	546.62	544.9	0.0006		
10-24	2-(carboxymethoxy)-5-{(2S)-2-{[3-(4-methoxyphenyl)propanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	576.65	575.0	0.0001		
10-25	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-[(4-oxo-4-phenylbutanoyl)amino]-3-[(4-phenylbutyl)amino]propyl}benzoic acid	574.63	573.1	0.0007	99	6.47
10-26	2-(carboxymethoxy)-5-{(2S)-2-{[(1-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	521.57	520.1	0.0002		
10-27	5-{(2S)-2-[(5-bromo-2-furoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	587.43	585.0	0.0007		
10-28	2-(carboxymethoxy)-5-{(2S)-2-(2-naphthoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	568.63	567.0	0.0005		
10-29	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[(2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]amino}propyl)benzoic acid	630.62	628.9	0.0001		

10-30	2-(carboxymethoxy)-5-{(2S)-2-{[(2R)-2-methoxy-2-phenylethanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	562.62	561.1	0.0005	99	6.6
10-31	2-(carboxymethoxy)-5-{(2S)-2-{[2-(4-fluorophenoxy)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	566.59	565.2	0.0005	95.2	6.78
10-32	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-[(2-phenylacetyl)amino]-3-[(4-phenylbutyl)amino]propyl}benzoic acid	532.60	531.2	0.0004	99	6.21
10-33	2-(carboxymethoxy)-5-{(2S)-2-{[2-(2-chlorophenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	567.04	565.1	0.0013	96.9	6.6
10-34	2-(carboxymethoxy)-5-{(2S)-2-{[2-(2-methoxyphenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	562.62	561.0	0.0003		
10-35	2-(carboxymethoxy)-5-{(2S)-2-{[2-(2-methylphenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	546.62	545.2	0.0007	99	6.6
10-36	2-(carboxymethoxy)-5-{(2S)-2-{[2-(3-chlorophenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	567.04	565.1	0.0005	99	6.84
10-37	2-(carboxymethoxy)-5-{(2S)-2-{[2-(3-methoxyphenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	562.62	561.0	0.0001	99	6.29
10-38	2-(carboxymethoxy)-5-[(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-({2-[3-(trifluoromethyl)phenyl]acetyl}amino)propyl]benzoic acid	600.59	599.0	0.0002	99	7.27
10-39	2-(carboxymethoxy)-5-{(2S)-2-{[2-(4-chlorophenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	567.04	565.0	0.0002		

10-40	2-(carboxymethoxy)-5-{(2S)-2-{[2-(4-methoxyphenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	562.62	561.0	0.0003	99	6.21
10-41	2-(carboxymethoxy)-5-[(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-({2-[4-(trifluoromethyl)phenyl]acetyl}amino)propyl]benzoic acid	600.59	598.9	0.0002		
10-42	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-[(4-phenylbutanoyl)amino]-3-[(4-phenylbutyl)amino]propyl}benzoic acid	560.65	559.1	0.0017		
10-43	2-(carboxymethoxy)-5-{(2S)-2-{[4-(4-methoxyphenyl)butanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	590.68	589.1	0.0005	99	6.89
10-44	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-[(5-oxo-5-phenylpentanoyl)amino]-3-[(4-phenylbutyl)amino]propyl}benzoic acid	588.66	586.9	0.0001		
155-45	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(5-phenylpentanoyl)amino]propyl}benzoic acid	574.68	573.0	0.0001		
10-46	2-(carboxymethoxy)-5-[(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-(10-undecenoylamino)propyl]benzoic acid	580.72	579.1	0.0005		
10-47	2-(carboxymethoxy)-5-{(2S)-2-{[(3-methyl-2-thienyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	538.62	537.0	0.0005	99	6.46
10-48	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[4-(2-thienyl)butanoyl]amino}propyl)benzoic acid	566.68	565.0	0.0004		
10-49	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-thienylcarbonyl)amino]propyl}benzoic acid	524.59	523.0	0.0004	99	5.93

10-50	5-{(2S)-2-[(1,3-benzodioxol-5-ylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	562.58	561.1	0.0002	95.9	6.19
10-51	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-quinolinylcarbonyl)amino]propyl}benzoic acid	569.62	568.0	0.0003	99	5.95
10-52	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-{[(2-oxo-2H-chromen-3-yl)carbonyl]amino}-3-[(4-phenylbutyl)amino]propyl}benzoic acid	586.60	585.0	0.0007	96.1	6.75
10-53	2-(carboxymethoxy)-5-{(2S)-2-{[4-(methylsulfonyl)benzoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	596.66	594.9	0.0001	99	5.62
10-54	2-(carboxymethoxy)-5-{(2S)-2-{[2-methoxy-4-(methylsulfanyl)benzoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	594.69	593.1	0.0013	97.4	7.02
10-55	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[2-(2-pyrimidinylsulfanyl)acetyl]amino}propyl)benzoic acid	566.63	565.0	0.0004		
10-56	2-(carboxymethoxy)-5-{(2S)-2-{[3-(4-chlorophenyl)propanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	581.07	579.0	0.0002	99	7.21
10-57	2-(carboxymethoxy)-5-{(2S)-2-{[2-(3,5-dimethoxyphenyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	592.65	590.9	0.0001	99	6.39
10-58	5-{(2S)-2-{[3-(1,3-benzodioxol-5-yl)propanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	590.63	589.1	0.0001	99	6.46
10-59	2-(carboxymethoxy)-5-{(2S)-2-{[(6-methyl-2-pyridinyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	533.58	532.0	0.0000		

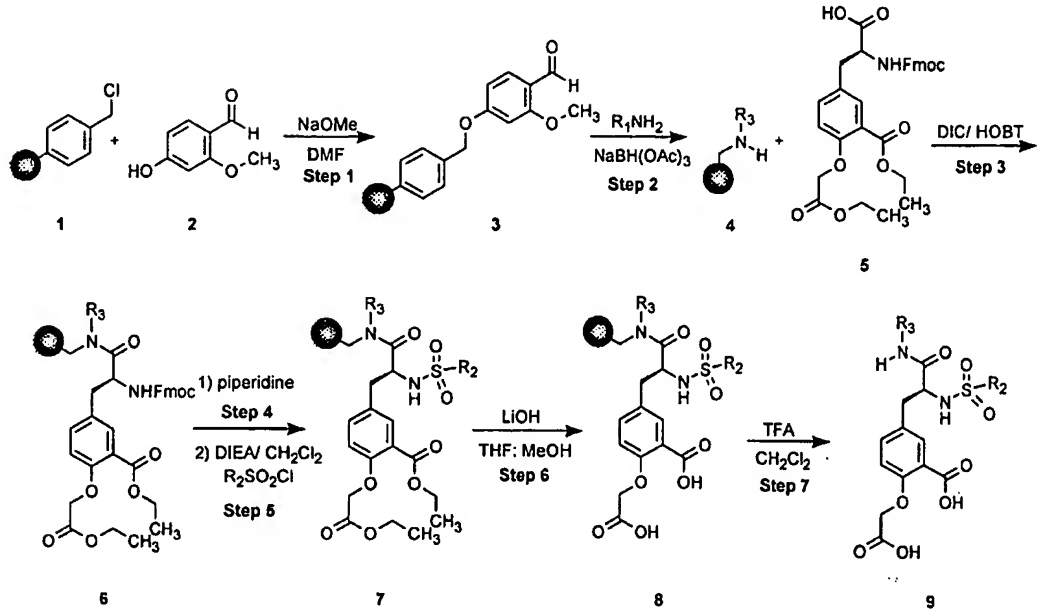
10-60	5-{(2S)-2-{[(1-acetyl-4-piperidinyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	567.64	566.0	0.0002		
10-61	2-(carboxymethoxy)-5-{(2S)-2-[(4-cyclohexylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	600.71	599.2	0.0014	99	9.01
10-62	2-(carboxymethoxy)-5-{(2S)-2-{[(5-chloro-2-thienyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	559.04	557.0	0.0002	99	7.07
10-63	2-(carboxymethoxy)-5-{(2S)-2-{[(3-methyl-1H-inden-2-yl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	570.64	569.0	0.0001	99	7.44
10-64	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(8-quinolinylcarbonyl)amino]propyl}benzoic acid	569.62	568.1	0.0011	96.9	6.4
10-65	2-(carboxymethoxy)-5-{(2S)-2-{[(3,5-dimethyl-4-isoxazolyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	537.57	536.0	0.0001	99	5.67
10-66	2-(carboxymethoxy)-5-{(2S)-2-{[(2,4-dimethyl-1,3-thiazol-5-yl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	553.64	554.0 (ES+)	0.0001		
10-67	2-(carboxymethoxy)-5-{(2S)-2-[[3-(4-fluorophenyl)propanoyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	564.61	563.1	0.0002	99	6.75
10-68	2-(carboxymethoxy)-5-{(2S)-2-{[(7-chloro-1-benzofuran-2-yl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	593.03	590.9	0.0007	99	7.57
10-69	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[(2S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl]amino}propyl)benzoic acid	630.62	629.0	0.0004		

10-70	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[[(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-yl)carbonyl]amino}propyl)benzoic acid	592.69	591.1	0.0009		
10-71	5-{(2S)-2-{[2-(3-acetyl-2,2-dimethylcyclobutyl)acetyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	580.68	579.1	0.0001	99	5.86
10-72	5-{(2S)-2-[(1-adamantylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	576.69	575.2	0.0014	96.1	7.72
10-73	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(tetrahydro-3-furanylcarbonyl)amino]propyl}benzoic acid	512.56	511.1	0.0004	99	4.74
10-74	2-(carboxymethoxy)-5-{(2S)-2-[(3-fluoro-2-methylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	550.59	549.2	0.0020	69.7	6.8
10-75	2-(carboxymethoxy)-5-{(2S)-2-[[(2,6-dimethoxy-3-pyridinyl)carbonyl]amino}-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	579.61	578.2	0.0029	98.7	6.69
10-76	2-(carboxymethoxy)-5-{(2S)-2-[(2,3-dihydro-1,4-benzodioxin-2-ylcarbonyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	576.61	575.0	0.0006	99	7.06/7.21
10-77	2-(carboxymethoxy)-5-{(2S)-2-[(2-fluoro-5-methylbenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid	550.59	549.2	0.0007	95.5	6.86
10-78	5-{(2S)-2-({2-[(1S,4S)bicyclo[2.2.1]hept-2-yl]acetyl}amino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	550.65	549.1	0.0004		
10-79	2-(carboxymethoxy)-5-{(2S)-3-oxo-2-[(2-phenoxypropanoyl)amino]-3-[(4-	562.62	561.2	0.0009	99	6.98/7.14

	phenylbutyl)amino]propyl}benzoic acid						
10-80	2-(carboxymethoxy)-5-[(2S)-3-oxo-2-({[(1R,2S,3S,4S)-5-oxotricyclo[2.2.1.0~2,6~]hept-3-yl]carbonyl}amino)-3-[(4-phenylbutyl)amino]propyl}benzoic acid	548.59		547.1	0.0012	99	5.15

EXAMPLE 11: Two-dimensional library of 5-substituted-2-carbomethoxybenzoic acids

Scheme 4



Chemistry Summary

The combination solid-phase/solution-phase synthetic sequence was designed to prepare a 6x10 two-dimensional library of 5-substituted-2-carboxymethoxybenzoic acids in a 96-well format as illustrated in Scheme 4. The synthesis was based on the use of the AMEBA linker (acid sensitive methoxybenzaldehyde, **3**), selected due to its ease of cleavage and versatility in the reductive amination step, and the intermediate **5**, synthesized in a seven step sequence as described below. The key resin **3** was synthesized by treating Merrifield resin with 2-methoxy-4-hydroxybenzaldehyde according to the literature procedure (Fivush, A.M.; Willson, T.M. *Tetrahedron Lett.* **1997**, *38*, 7151. Sarantakis, D.; Bicksler, J.J. *Tetrahedron Lett.*, **1997**, *38*, 7325). The functionalized resin **3** was treated with the first diversity element, a primary amine, and sodium triacetoxyborohydride to provide six different secondary amine resins, **4**. Attachment of **5** to each individual resin was performed utilizing the standard conditions of DIC/HOBt in DMF. A deprotection/ sulfonamide formation (Kim, S.W.; Hong, C.Y.; Lee, K.; Lee, E.J.; Koh, J.S. *Bio. and Med. Chem. Letters.* 1998, *8*, 735) protocol was followed to attach the next diversity element to give **7**. Hydrolysis of the diester was then followed by removal of the products from the resin with 20% TFA/CH_2Cl_2.

Intermediate Synthesis

Scaffold 5 (see Scheme 4 above), (2S)-3-[3-ethyoxycarbonyl)-4-(2-ethoxy-2-oxoethoxy)phenyl]-2-{[(9H-fluoren-9-ylmethoxy)carbonyl]amino}propanoic acid, was prepared as described in Example 9 above.

Diversity Elements

N-Terminal Sulfonyl Chlorides (commercially available):

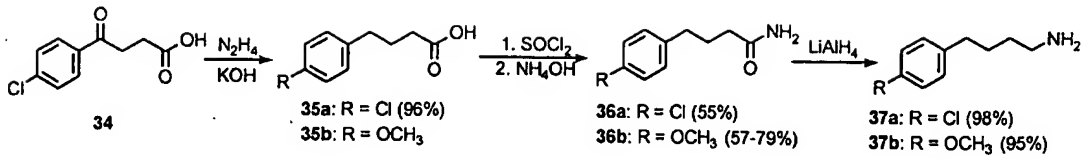
Name	Cpd #
benzene sulfonyl chloride	**18**
2,4-difluorobenzene sulfonyl chloride	**19**
1-methylimidazole-4-sulfonyl chloride	**20**
4-(n-butoxy)benzene sulfonyl chloride	**21**
naphthalene sulfonyl chloride	**22**
2-nitrobenzene sulfonyl chloride	**23**
octane sulfonyl chloride	**24**
8-quinoline sulfonyl chloride	**25**
2,3,5,6-tetramethylbenzene sulfonyl chloride	**26**
trans-β-styrene sulfonyl chloride	**27**
N-acetylsulfanilylchloride	**28**
benzo-2,1,3-thiadiazole-4-sulfonyl chloride	**29**
4-cyanobenzene sulfonyl chloride	**30**
3,4-dimethoxybenzene sulfonyl chloride	**31**

C-Terminal Amines:

a) Commercially available:

Name	Cpd #
n-amylamine	**32**
4-phenylbutylamine	**33**

b) Synthesized



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35a: R = Cl (96%)
35b: R = OCH_3

36a: R = Cl (55%)
36b: R = OCH_3 (57-79%)

37a: R = Cl (98%)
37b: R = OCH_3 (95%)

Two of the six amines used in this library were commercially available, the remaining four amines **37a, 37b, 39** and **44** were prepared synthetically. Wolff-Kishner reduction of 4-(p-chlorophenyl)-4-oxobutanoic acid gave 4-(p-chlorophenyl)butanoic acid (**35a**) in 96% yield, which was converted to **36a** (55%). 4-(p-Methoxyphenyl)butylamine (**37b**) was similarly synthesized with equal results from commercially available **35b**. Benzyl ethylamine ether (**39**) was prepared in one step from ethanolamine and benzyl chloride in 10% yield.

4-(p-chlorophenyl)butanoic acid (35a). A mixture of 3-(4-chlorobenzoyl) propionic acid (**34**) (2.50 g, 12.0 mmol), KOH (s) (1.75 g, 31.2 mmol), and hydrazine monohydrate (1.25 mL, 25.8 mmol) in 12.5 mL of diethylene glycol was refluxed azeotropically at 120-130°C for 90 min to remove water. The reaction mixture was then refluxed at 170°C for 3 h, cooled to RT, diluted with 12.5 mL of water, and poured into 15 mL 2.5 N HCl(aq). The precipate was filtered off, dissolved in CH_2Cl_2, and the solvent removed to give **35a** (2.23 g, 96%) as a white solid. UV λ_{max} 223(8980, 95% ETHANOL); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 7 Hz, 2 H), 7.12 (d, J = 8 Hz, 2 H), 2.66 (t, J = 4 Hz, 2 H), 2.38 (t, J = 4 Hz, 2 H), 1.96 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 179.3, 140.0, 132.2, 130.2, 128.9, 34.7, 33.4, 26.4; IR (drift) 3063 (s), 3051 (s), 2955 (s), 2923 (s,b), 2905 (s), 2814, 2797, 2493 (b), 2466, 2413, 2367 (b), 2321, 1706 (s), 1492 (s), 1212 (s), cm^{-1}; MS (EI) m/z (rel. intensity) 198 (M+, 22), 200 (7), 198 (22), 140 (32), 139 (17), 138 (99), 127 (15), 125 (48), 103 (10), 89 (13), 60 (9); HRMS (EI) calcd for 198.0448, found 198.0441.

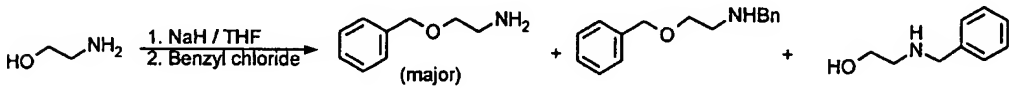
4-(p-chlorophenyl)butanamide (36a). A mixture of **35a** (1.880 g, 10.1 mmol) and thionyl chloride (3.0 mL, 40.9 mmol) in 15 mL $CHCl_3$ was stirred at reflux (75°C) for 4 h. Solvent and excess thionyl chloride were removed *in vacuo*, and residue was twice diluted with 7.5 mL toluene and evaporated to remove traces of thionyl chloride. To a solution of the residue in 3 mL toluene was slowly added 9 mL of cold concentrated NH_4OH. The precipitate was filtered off and recrystallized in $CHCl_3$/heptane to give **36a** (1.02 g, 55%) as a white solid. UV λ_{max} 224 (9300, 95% ETHANOL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8 Hz, 2 H), 7.12 (d, J = 8

Hz, 2 H), 5.31 (s, 2H), 2.66 (t, J = 8 Hz, 2 H), 2.23 (t, J = 7 Hz, 2 H), 1.98 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.4, 140.2, 134.5, 130.2, 128.9, 35.1, 34.8, 27.0; IR (drift) 3434, 2948, 2282 (w), 1901 (w), 1655 (s), 1607, 1491, 1420, 1306, 1094, 1016, 836 (s), 825, 804, 666, cm^{-1}. Calcd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09; Cl, 17.94. Found: C, 60.60; H, 6.11; N, 6.96.

4-(p-chlorophenyl)butylamine (37a). (Ali, F.E.; Dandridge, P.A.; Gleason, J.G.; Krell, R.D.; Kruse, C.H.; Lavanchy, P.G; Snader, K.M. *J. Med. Chem.*, **1982**, *25*, 947). To a stirred suspension of lithium aluminum hydride (2.40 g, 63.2 mmol) in 65 mL diethyl ether was added slowly a solution of (3.12 g 15.8 mmol) of **36a** in 28 mL THF, and stirred at rt for 1 h. To the reaction mixture was slowly added 4 mL water, 4 mL 5 N NaOH(aq), and 12 mL water. The organics were removed from the emulsion which was dissolved in water and extracted with ether. The organic portions were dried over Na_2SO_4(s), and condensed to give **37a** (2.76 g, 95%) as an oil. UV λ_{max} 224 (7600, 95% ETHANOL). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 2 H), 7.10 (d, J = 8 Hz, 2 H), 2.74 (t, J = 7 Hz, 2 H), 2.60 (t, J = 8 Hz, 2 H), 2.25 (s, 2 H), 1.64 (m, 2 H), 1.49 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 141.2, 131.8, 130.1, 128.8, 42.3, 35.4, 33.6, 29.0; IR (liq.) 3365 (b), 3296 (b), 3026, 2933 (s), 2858 (s), 2170 (w), 1996 (w), 1576, 1492 (s), 1460, 1093 (s), 1016 (s), 831, 821, 804, cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{14}ClN$ +H_1 184.0893, found 184.0879.

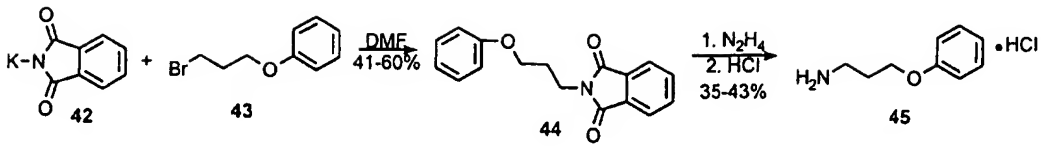
4-(p-methoxyphenyl)butanamide (36b). A mixture of 4-(p-methoxyphenyl)butyric acid (**35b**) (6.50 g, 33.5 mmol) and thionyl chloride (10.0 mL, 137 mmol) in 50 mL $CHCl_3$ was stirred at reflux for 5.5 h. Solvent and excess thionyl chloride were removed *in vacuo*, and residue was twice diluted with 25 mL toluene and evaporated to remove traces of thionyl chloride. To a solution of the residue in 10 mL toluene was added slowly 30 mL of cold concentrated NH_4OH. The precipitate was filtered off and recrystallized in $CHCl_3$/heptane to give **36b** (3.68 g, 57%) as a white solid. UV λ_{max} 223 (10200, 95% EtOH); ^{1}H NMR (400 MHz, CDCl3) δ 7.10 (d, J = 9 Hz, 2 H), 6.84 (d, J = 9 Hz, 2 H), 5.44 (s, 2 H), 3.80 (s, 3 H), 2.63 (t, J = 7 Hz, 2 H), 2.23 (d, J = 8 Hz, 2 H), 1.96 (m, 2 H); 13C NMR (CDCl3) δ 175.5, 158.3, 133.8, 129.7, 114.2, 55.6, 35.4, 34.5, 27.4; IR (drift) 3366 (s), 2479 (w), 2355 (w), 2285 (w), 2053 (w), 1993 (w), 1656 (s), 1628 (s), 1512 (s), 1416 (s), 1304 (s), 1243 (s), 1230 (s), 1031 (s), 838 (s), cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.42; H, 8.03; N, 7.24.

4-(p-methoxyphenyl)butylamine (37b). (Ali, F.E.; Dandridge, P.A.; Gleason, J.G.; Krell, R.D.; Kruse, C.H.; Lavanchy, P.G; Snader, K.M. *J. Med. Chem.*, **1982**, *25*, 947). To a stirred suspension of lithium aluminum hydride (4.40 g, 116 mmol) in 120 mL diethyl ether was added dropwise a solution of **36b** (5.60 g, 29.0 mmol) in 10 mL THF, and stirred at rt for 1 h. To the reaction mixture was added 7.5 mL water, 7.5 mL 5 N NaOH(aq), and 20 mL water. The organics were removed from the emulsion which was dissolved in water and extracted with ether. The organic portions were dried over Na_2SO_4(s), and condensed to give **37b** (5.10 g, 98%) as an oil. UV λ_{max} 223 (9410, 95% EtOH). (400 MHz, $CDCl_3$) δ 7.10 (d, J = 9 Hz, 2 H), 6.83 (d, J = 9 Hz, 2 H), 3.79 (s, 3 H), 2.71 (t, J = 7 Hz, 2 H), 2.58 (t, J = 7 Hz, 2 H), 1.63 (m, 2 H), 1.48 (m, 2 H); IR (liq.) 2933 (s), 2856, 2145 (w), 2059 (w), 1996 (w), 1612 (s), 1584, 1513 (s), 1461, 1442, 1246 (s), 1178, 1034 (s), 827, 822, cm^{-1} HRMS (FAB) calcd for $C_{11}H_{17}NO$ $+H_1$ 180.1388, found 180.1387.



38 39 40 41

2-(benzyloxy)ethylamine (39). (Hu, X.E.; Cassady, J.M. *Synthetic Comm.*, **1995**, *25*, 907). To a solution of distilled ethanolamine (**38**) (1.81mL, 30.0 mmol) in 30 mL of dry THF, was added NaH (1.2 g 30.0 mmol) as a 60% dispersion in mineral oil, in small portions at rt. The mixture was stirred at reflux for 30 min., benzyl chloride (2.88 mL, 25.0 mmol) was added, and stirred at reflux for an additional 4.5 h. The mixture was cooled to rt, 10 mL water was added, and solvent evaporated *in vacuo*. The residue was partitioned between 1 N HCl(aq) and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 to remove side product **40**. The aqueous portion was adjusted to pH 13 with 10% NaOH(aq) and extracted with CH_2Cl_2. The extracts were condensed and purified by flash chromatography (10% MeOH(saturated with NH_3)/CH_2Cl_2) to give **39** (0.24 g, 10%) as a yellow oil. R_f(10% MeOH(saturated with NH_3)/CH_2Cl_2) = 0.47; UV λ_{max} 251 (162, 95% ETHANOL); 1H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.55 (s, 2 H), 3.53 (t, J = 5 Hz, 2 H), 2.90 (t, J = 5, 2 H), 1.68 (s, 2 H); ^{13}C NMR (CDCl3) δ 138.7, 128.8, 128.1, 128.0, 73.5, 72.9, 42.3; IR (liq.) 3371, 3302 (b), 3030, 2924 (b), 2860 (s), 2202 (w), 1955 (w), 1496, 1453 (s), 1356, 1101 (s), 1069, 1028, 739 (s), 698 (s), cm^{-1}. HRMS (FAB) calcd for $C_9H_{13}NO$ $+H_1$ 152.1075, found 152.1074.



42 43 44 45

3-Phenoxypropylphthalimide (44). A mixture of 7.41 g (40.0 mmol) of potassium phthalimide and 6.30 mL (40.0 mmol) of 3-phenoxypropylbromide in 100 mL DMF was stirred at reflux (165°C) under N_2(g) for 90 min. Mixture was cooled and filtered, filtrate was condensed *in vacuo*. Residue was recrystallized from 95% ethanol to give **44** (6.68 g, 58%) as a white solid. UV λ_{max} 222 (41700, 95% ETHANOL). ^{1}H NMR (400 MHz, CDCl3) δ 7.85 (m, 2 H), 7.72 (m, 2 H), 7.24 (t, J = 10 Hz, 2 H), 6.92 (t, J = 7 Hz, 4 H), 6.82 (d, J = 4 Hz, 2 H), 4.03 (t, J = 6 Hz, 2 H), 3.92 (t, J = 4 Hz, 2 H), 2.20 (t, J = 3 Hz, 2 H); ^{13}C NMR (CDCl3) δ 168.7, 134.7, 134.3, 132.6, 129.7, 124.0, 123.6, 121.1, 114.9, 65.9, 35.9, 28.7; IR (drift) 2474 (w), 2431 (w), 2417 (w), 2339 (w), 2305 (w), 1770, 1705 (s), 1600, 1397, 1388, 1249 (s), 1233, 756, 721 (s), 712, cm^{-1}. HRMS (FAB) calcd for $C_{17}H_{15}NO_3$+H_1 282.1130, found 282.1129.

3-Phenoxypropylamine hydrochloride(45). (Lever, O.W., Jr.; Bell, L.N.; McGuire, H.M.; Ferone, R. *J. Med. Chem.*, **1985**, *28I*, 1873). A mixture of 6.95 g (24.8 mmol) of **44** and 3.12 mL (99.3 mmol) of 98% hydrazine in 80 mL 95% ethanol was stirred at reflux (85°C) under N_2(g) for 3 h. Mixture was cooled and white precipitate was dissolved in 250 mL water, mixed with 20 mL 10% NaOH(aq), extracted with diethyl ether. Ether extracts were washed with water, acidified with 60 mL 1 N HCl(aq), and condensed *in vacuo*. Residue was recrystallized from ethanol-ether to give **45** (2.02 g, 43%) as a white solid. UV λ_{max} 222 (41700, 95% ETHANOL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s), 7.29 (t, J = 4 Hz, 2 H), 6.93 (m, 3 H), 4.05 (t, J = 3 Hz, 2 H), 3.31 (s, 2 H), 2.94 (s, 2 H), 2.02 (m, 2 H); ^{13}C NMR (DMSO-d6) δ 159.1, 130.3, 121.5, 115.3, 65.3, 37.1, 27.7; IR (drift) 3036 (s), 3029 (s,b), 3009 (s,b), 2963 (s,b), 2938 (s), 2925 (s), 2428 (w), 2351 (w), 2256 (w), 2203 (w), 2052 (w), 1598 (s), 1258 (s), 749 (s), 696 (s), cm^{-1}. Anal. Calcd for $C_9H_{13}NO$.HCl: C, 57.60; H, 7.52; N, 7.46; Cl, 18.89. Found: C, 57.45; H, 7.75; N, 7.36.

Library Synthesis

The production of the library required seven steps using solid support. Three steps were carried out in a 96 well format. The AMEBA (acid sensitive methoxy benzaldehyde) linker was prepared by reacting Merrifield resin and 4-hydroxy-2-methoxybenzaldehyde with sodium methoxide (see Scheme 4). The AMEBA resin was then treated with the corresponding amine and $NaBH(OAc)_3$ to give the corresponding reductive amination product. The tyrosine scaffold (**5**) was then coupled to the various amine resins using DIC and HOBT in DMF. The Fmoc protecting group was then removed with piperidine/ DMF (1:1). The resin was then plated in a 96 well Robbins block then coupled to the corresponding sulfonyl chloride with DIEA in CH_2Cl_2. The diethyl ester was hydrolyzed with excess LiOH in THF: MeOH (1:1) for 16 h at rt to yield the dicarboxylic acid on resin. The use of THF : MeOH (1:1) is believed to be crucial for this hydrolysis. The product was then cleaved from the resin with 20% TFA / CH_2Cl_2 solution. The resin was cleaved twice to yield the maximum possible product. The second cleavage resulted in approximately 10-20% more product without any change in purity levels.

Step 1: Preparation of AMEBA Linker A suspension of Merrifield resin (2.10g, 3.47 mmol) in 50 mL of DMF was treated with solid sodium methoxide (560 mg, 10.4 mmol). To the solution was added 4-hydroxy-2-methoxybenzaldehyde (1.58 g, 10.4 mmol). The reaction mixture was heated to 60-70°C for 24 h. The resin was then washed with DMF, MeOH, water, MeOH, CH_2Cl_2, and MeOH (3x 10 mL). IR indicated strong absorption at 1681 cm^{-1}.

Step 2: Reductive Amination A suspension of AMEBA (1.04g 1.12 mmol) in 25 mL of $C_2H_4Cl_2$ was treated with phenylbutyl amine (0.36 mL, 2.3 mmol) and $NaBH(OAc)_3$ (479 mg, 2.26 mmol). The reaction mixture was stirred at rt for 3 h. The resin was then washed with CH_2Cl_2, DMF, MeOH and CH_2Cl_2 (3x 10 mL). IR indicated disappearance of strong absorption at 1681 cm^{-1}.

Step 3: Coupling Resin to Intermediate 5 A suspension of resin (734 mg, 0.751 mmol) in 20 mL of DMF was treated with tyrosine scaffold **5** (632 mg, 1.13 mmol), hydroxybenzotriazole (HOBT) (24 mg, 0.18 mmol), diisopropyl carbodiimide (DIC) (175 µL, 1.12 mmol). The reaction mixture was stirred at rt for 2 h. The resin was tested for the presence of any secondary amine using the choranil test. A sample of resin 1-5 mg was mixed with one drop of 2% acetaldehyde in DMF and one drop of 2% chloranil in DMF. After 5 min the resin showed no

color change; a control containing a secondary amine stained blue (Vojkovsky T. *Peptide Research* **1995**, *4*, 236). The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 10 mL).

Step 4: Fmoc Removal Resin (1.14 g, 0.751 mmol) was suspended in 10 mL of piperidine/ DMF (1:5) and stirred for 30 min. at rt. The resin was washed with DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (3x 10 mL).

Step 5: Coupling Resin to Sulfonyl Chloride

The resin was plated in a 96 well Robbins block (approx. 62 mg, 0.045 mmol), added to each well as a slurry in DMF/ CH_2Cl_2. The resin was filtered and dried. Standard solutions of sulfonyl chloride (0.9 M in CH_2Cl_2)and DIEA (1.8 M in CH_2Cl_2) were prepared. To the resin in each well was added 0.5 mL CH_2Cl_2, 0.25 mL DIEA solution, and then 0.25 mL of the standard sulfonyl chloride solution. The Robbins block was then rotated at rt for 2.5 h. The resin was filtered and washed with CH_2Cl_2, DMF, MeOH (2x 1 mL), then 1 mL CH_2Cl_2.

Step 6: Hydrolysis of Esters

A standard solution of LiOH (0.9 M in 1:1 THF/MeOH) was prepared. The resin in each well was treated with 1 mL of standard LiOH solution. The Robbins block was rotated at rt for 16 h. The resin was filtered and washed with CH_2Cl_2, DMF, MeOH (2x 1 mL), then 1 mL CH_2Cl_2.

Step 7: Cleavage

The resin (approx. 62 mg, 0.045 mmol) in each well was treated with 0.50 mL of TFA/ CH_2Cl_2 (1:5). The Robbins block was rotated for 30 min. The resin was washed with CH_2Cl_2 (0.75 mL) collecting the filtrate. Resin was rinsed a second time into a second collection plate with CH_2Cl_2 (1.0 mL).

Purification

The entire library was purified by reverse phase HPLC. Half of the library was, however, lost during purification. The average purity, based on four original and six different standards, after purification of the library average purity was 75±13% by analytical HPLC. The average yield after purification was 10% (1-2 mg per well on average). The preparative HPLC system used a Gilson 215 liquid robotics autosampler/fraction collector. The chromatography utilized a

three-pump system of Rainin pump heads equipped with 10 mL/min or 50 mL/min pump solvent delivery heads and a Gilson solvent mixing chamber. Two pumps were used for solvent delivery, and one was used for flushing the system at the completion of the series of chromatography runs. UV absorbance was monitored using a Knauer variable wavelength UV detector equipped with a 10 mm path length analytical flow cell. The entire system was controlled by Gilson Unipoint software v. 1.65 which was used for data acquisition and analysis.

Samples were prepared for injection by dissolving each in 1 mL MeOH and housing them in 96-well microtiter plates (2 mL/well). Injections for the chromatography loaded the entire sample into a 2.0 mL injection loop installed on the Gilson 819/Rheodyne Injector Module.

The HPLC method used in this study is as follows:

Column:	YMC GuardPack C8 (20 X 50 mm, 5 μ, 120 A)
Mobile A:	water + 0.05% trifluoroacetic acid (TFA)
Mobile B:	acetonitrile
Flow Rate.	10 mL/ min
Gradient:	10% B 0-2 min, 10-100% B 2-23 min, 100% B 23-25 min, re-equilibrate for 3 min
Detection:	UV absorbance at 220 nm, Knauer UV detector with 10 mm flow cell
Fraction Collection:	Gilson 215, 15% AUFS threshold, 9 mL maximum/tube in 13 X 100 mm disposable tubes

Mass Spectrometry

Each of the recovered compounds was analyzed by mass spectrometry after reverse phase HPLC. Only 28 compound having a covered mass greater than 0.1 mg were positively identified by a molecular ion peak.

Library Compounds (Examples 11-1 to 11-28)

The following compounds were obtained in the library

Table C

Ex. No.	Compound Name	Mol Wt.	MS (ES+) Ion Observed	Mass Recovered, g	Final HPLC Purity at 220 nm	Retention Time, min
11-1	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(2,4-difluorophenyl)sulfonyl]amino}-3-oxopropyl)benzoic acid	625.05	626.3	0.0014		
11-2	5-((2S)-2-{[(4-butoxyphenyl)sulfonyl]amino}-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	661.17	662.4	0.0015		
11-3	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-[(1-naphthylsulfonyl)amino]-3-oxopropyl}benzoic acid	639.13	640.3	0.0018		
11-4	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(2-nitrophenyl)sulfonyl]amino}-3-oxopropyl)benzoic acid	634.06	635.3	0.0015		
11-5	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-[(8-quinolinylsulfonyl)amino]propyl}benzoic acid	640.11	641.2	0.0018		
11-6	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-{[(2,3,5,6-tetramethylphenyl)sulfonyl]amino}propyl)benzoic acid	645.17	646.4	0.0009	78.316	5.71
11-7	2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-({[(E)-2-phenylethenyl]sulfonyl}amino)propyl]benzoic acid	615.10	616.3	0.0009	59.937	5.32
11-8	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-[(phenylsulfonyl)amino]propyl}benzoic acid	584.65	585.2	0.0014	82.814	4.55
11-9	2-(carboxymethoxy)-5-((2S)-2-{[(2,4-	620.63	621.2	0.0018	83.333	4.70

	difluorophenyl)sulfonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid						
11-10	5-((2S)-2-{[(4-butoxyphenyl)sulfonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	656.75	657.2	0.0015			
11-11	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-2-[(1-naphthylsulfonyl)amino]-3-oxopropyl}benzoic acid	634.71	635.2	0.0010			
11-12	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-2-{[(2-nitrophenyl)sulfonyl]amino}-3-oxopropyl)benzoic acid	629.65	630.1	0.0011			
11-13	2-(carboxymethoxy)-5-{(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-[(8-quinolinylsulfonyl)amino]propyl}benzoic acid	635.70	636.2	0.0020	71.512	4.48	
11-14	2-(carboxymethoxy)-5-((2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-{[(2,3,5,6-tetramethylphenyl)sulfonyl]amino}propyl)benzoic acid	640.76	641.2	0.0012			
11-15	2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxo-2-({[(E)-2-phenylethenyl]sulfonyl}amino)propyl]benzoic acid	610.69	611.2	0.0011			
11-16	2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(3-phenoxypropyl)amino]-2-[(phenylsulfonyl)amino]propyl}benzoic acid	556.59	557.2	0.0012			
11-17	2-(carboxymethoxy)-5-{(2S)-2-{[(2,4-difluorophenyl)sulfonyl]amino}-3-oxo-3-[(3-phenoxypropyl)amino]propyl}benzoic acid	592.57	593.1	0.0002			
11-18	5-{(2S)-2-{[(4-butoxyphenyl)sulfonyl]amino}-3-oxo-3-[(3-phenoxypropyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	628.70	629.2	0.0010	98.744	not available	
11-19	2-(carboxymethoxy)-5-{(2S)-2-[(1-naphthylsulfonyl)amino]-3-oxo-3-[(3-	606.65	607.2	0.0007			

	phenoxypropyl)amino]propyl}benzoic acid					
11-20	2-(carboxymethoxy)-5-{(2S)-2-{[(2-nitrophenyl)sulfonyl]amino}-3-oxo-3-[(3-phenoxypropyl)amino]propyl}benzoic acid	601.59	602.1	0.0010	95.316	4.48
11-21	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(3-phenoxypropyl)amino]-2-{[(2,3,5,6-tetramethylphenyl)sulfonyl]amino}propyl)benzoic acid	612.70	613.2	0.0006		
11-22	2-(carboxymethoxy)-5-((2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-{[(2,3,5,6-tetramethylphenyl)sulfonyl]amino}propyl)benzoic acid	610.73	611.2	0.0005	41.633	not available
11-23	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-[(phenylsulfonyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	556.59	557.2	0.0012		
11-24	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-2-{[(2,4-difluorophenyl)sulfonyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	592.57	593.1	0.0004		
11-25	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-2-[(1-naphthylsulfonyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid	606.65	607.1	0.0002	85.214	4.13
11-26	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-2-{[(2-nitrophenyl)sulfonyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid	601.59	602.2	0.0008		
11-27	5-{(2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-[(8-quinolinylsulfonyl)amino]propyl}-2-(carboxymethoxy)benzoic acid	607.64	608.2	0.0003		
11-28	5-((2S)-3-{[2-(benzyloxy)ethyl]amino}-3-oxo-2-{[(2,3,5,6-tetramethylphenyl)sulfonyl]amino}propyl)-2-(carboxymethoxy)benzoic acid	612.70	613.2	0.0002		

EXAMPLE 12

General Methods. NMR spectra were recorded on a Varian spectrometer and chemical shifts are given in ppm using CD_3OD d 3.31 as an internal standard at 25 °C. Only selected data are reported. HPLC analysis was performed using a Hypersil C-18 column (50 x 4.6 mm, 3 m) with a flow of 1 ml/min on a HP 1100 system with monitoring at 214 and 254 nm. For preparative HPLC purification a Vydac C-18 column (250 x 22 mm, 10u) was used on a Gilson system with a flow of 15 ml/min. LCMS chromatograms and spectra were recorded on a Perkin Elmer Sciex system using a YMC-Pack FL-ODS column (50 x 4.6 mm, 5 u, 120A) with a flow of 4 ml/min. IR spectra were recorded on a Perkin Elmer Spectrum 1000 FTIR spectrometer. HRMS and FRMS spectra were recorded on a LCT instrument with electrospray.

Synthetic Method A. (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) was weighed into 10 screw-capped tubes and dissolved in dichloromethane (500 uL). 1-Hydroxybenzotriazole (0.23 mmol) in dimethylformamide (100 uL) was added to each tube followed by a set of 10 amines (0.29 mmol). The mixtures were cooled in an ice bath and 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (0.23 mmol) in dichloromethane (2 mL) was added to each tube. The mixtures were left in room temperature for 3h and were then applied on small silica gel columns (5 ml) packed in dichloromethane. The products were eluted with dichloromethane followed by, dichloromethane-acetonitrile (1:1) and finally acetonitrile. The amide containing fractions were concentrated and dried under vacuum. The amides were then dissolved in tetrahydrofuran-methanol (2:1, 3 mL) and sodium hydroxide (1.5 mL, 2%, aq) was added. The mixtures were shaken at room temperature 5-7 h. Acetic acid (40 uL) was added and the mixtures were concentrated until approximately 2 mL was left in each tube. The materials were analyzed by HPLC and LC-MS and were then purified by reversed phase HPLC (Vydac C-18 column) using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. After HPLC analysis the purest fractions were collected and lyophilized.

Synthetic Method B. To eight solutions of (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) in dichloromethane (500 uL) in

screw-capped tubes was added a set of eight amines (0.29 mmol). 1-Hydroxybenzotriazole (0.23 mmol) in dimethylformamide (100 uL) was added and the mixtures were cooled in an ice bath. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 mmol) in dichloromethane (2 ml) was added to each tube and the reaction mixtures were left in room temperature over night. The mixtures were then applied on small silica gel columns (6 ml) packed in chloroform. The products were eluted with a step-wise chloroform-methanol gradient. The amide containing fractions were concentrated and dried under vacuum. The amides were then dissolved in methanol (1 mL) and sodium hydroxide (1.2 mL, 2%, aq) was added. When necessary tetrahydrofuran (500 uL) was added. The mixtures were left in room temperature for 5-7 h. Dowex H+ was added and after analysis by HPLC and LC/MS the materials were purified by reversed phase HPLC (Vydac C-18 column) using acetonitrile-water gradients. After HPLC analysis the purest fractions were collected and lyophilized.

Synthetic Method C. (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (typically 100 mg, 1 eq) was weighed into 10 screw-capped tubes and dissolved in dichloromethane (500 uL). A set of 10 amines (1.2 eq) was dissolved in dichloromethane (1 mL) and triethylamine (2 equivalents to the amines) was added. The amine solutions were added to the carboxylic acid solutions and the mixtures were cooled in an ice bath. 1-Hydroxybenzotriazole (1.2 eq) in dimethylformamide (100 uL) was added followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 mmol) in dichloromethane (2 mL). The mixtures were left in room temperature over night. The mixtures were then applied on small silica gel columns (5-7 ml) packed in chloroform. The products were eluted with a stepwise chloroform-methanol gradient. The amide containing fractions were concentrated and dried under vacuum. The amides were then dissolved in tetrahydrofuran-methanol (1:1, 2 mL) and sodium hydroxide (1 mL, 2%, aq) was added. The mixtures were left in room temperature over night. Dowex H+ was added and the mixtures were concentrated until approximately 2 mL was left. The materials were either lyophilized directly or purified by reversed phase HPLC (Vydac C-18 column) using acetonitrile-water gradients. After HPLC analysis the purest fractions were collected and lyophilized.

Example 12-1: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylpropyl)amino]propyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 3-pnenylpropylamine (41 uL) according to Method A to give the title compound (48 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.79 (s, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.26-7.13 (m, 10H), 6.99 (d, J=8.5 Hz, 1H), 4.72 (s, 2H), 4.52 (t, J=6.8 Hz, 1H), 4.25 (dd, J=5.3 Hz, J=9.2 Hz, 1H), 3.18 (m, 1H), 3.09-2.92 (m, 4H), 2.77 (dd, J=9.5 Hz, J=13.5 Hz, 1H), 2.50 (t, J=7.7 Hz, 2H), 1.69 (m, 2H), 1.34 (s, 9H); IR (KBr) 3302, 2926, 1736, 1686, 1646 cm^{-1}; HRMS m/z 647.2823 (calc. of monoisotopic mass for $C_{35}H_{41}N_3O_9$ gives 647.2823).

Example 12-2: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 4-phenylbutylamine (46 uL) according to Method A to give the title compound (34 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.38 (d, J=8.5 Hz, 1H), 7.26-7.11 (m, 10H), 6.98 (d, J=8.5 Hz, 1H), 4.76 (s, 2H), 4.50 (t, J=6.9 Hz, 1H), 4.23 (dd, J=5.2 Hz, J=9.3 Hz, 1H), 3.17 (m, 1H), 3.09-2.91 (m, 4H), 2.75 (dd, J=9.4 Hz, J=13.6 Hz, 1H), 2.58 (t, J=7.5 Hz, 2H), 1.54 (m, 2H), 1.42 (m 2H), 1.34 (s, 9H); IR (KBr) 3296, 2925, 1738, 1687, 1643 cm^{-1}; HRMS m/z 661.2987 (calc. of monoisotopic mass for $C_{36}H_{43}N_3O_9$ gives 661.2999).

Example 12-3: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(2-hydroxyethyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic

Synthesis was performed from PNU-181049 and ethanolamine (18 uL) according to Method A to give the title compound (58 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.41 (d, J=8.6 Hz, 1H), 7.27-7.17 (m, 5H), 7.02 (d, J=8.5 Hz, 1H), 4.80 (s, 2H), 4.55 (m, 1H), 4.24 (dd, J=5.0 Hz, J=9.4 Hz, 1H), 3.52 (m, 2H), 3.25 (m, 2H), 3.10 (dd, J=6.1 Hz, J=13.7 Hz, 1H), 3.02 (dd, J=4.9 Hz, J=13.9 Hz, 1H), 2.95 (dd, J=7.9 Hz, J=13.8 Hz, 1H), 2.74 (dd, J=9.5 Hz, J=13.4 Hz, 1H), 1.35 (s, 9H); IR (KBr) 3339, 3298, 2961, 1743, 1714,

1686 cm^{-1}; HRMS m/z 573.2325 (calc. of monoisotopic mass for $C_{28}H_{35}N_3O_{10}$ gives 573.2322).

Example 12-4:-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(2,3-dihydroxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 3-amino-1,2-propanediol 22 (uL) according to Method A to give the title compound (46 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.78 (s, 1H), 7.42 (d, J=8.3 Hz, 1H), 7.28-7.20 (m, 5H), 7.03 (d, J=8.5 Hz, 1H), 4.81 (s, 2H), 4.57 (m, 1H), 4.24 (dd, J=4.8 Hz, J=9.3 Hz, 1H), 3.69-3.56 (m, 2H), 2.74 (dd, J=9.0 Hz, J=13.4 Hz, 1H), 1.34 (s, 9H); IR (KBr) 3292, 2932, 1686, 1652 cm^{-1}; HRMS m/z 603.2412 (calc. of monoisotopic mass for $C_{29}H_{37}N_3O_{11}$ gives 603.2428).

Example 12-5: Disodium 5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(1-phenylethyl)amino]propyl}-2-(2-oxido-2-oxoethoxy)benzoate

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 1-phenylethylamine (38 uL) according to Method A to give a material which was re-purified by reversed phase C-18 HPLC in absence of trifluoroacetic acid and then passed through a column with Dowex Na+. After lyophilizing, the title compound (34 mg) was obtained as a diasteromeric mixture with a 2:1 ratio of the components (HPLC). (KBr) 3291, 2971, 1691, 1642 cm^{-1}; HRMS m/z 633.2682 (calc. of monoisotopic mass for $C_{34}H_{39}N_3O_9$ gives 633.2686).

Example 12-6: 5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[1-(hydroxymethyl)pentyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and D,L-2-amino-1-hexanol (37 uL) according to Method A with the difference that after the hydrolysis, the reaction mixture was neutralized by Dowex H+ . Thereafter the obtained solution was lyophilized to give the title compound (95 mg) as a diasteromeric mixture with a 1:1 ratio of the components (HPLC). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.40 (d, J=8.5 Hz, 1H), 7.27-7.17 (m, 5H), 7.02 (d, J=8.5 Hz, 1H), 4.82 (s, 2H), 4.51 (t, J=6.8 Hz, 1H), 4.23 (m, 1H), 3.16 (m, 1H), 2.76 (dd, J=9.3 Hz, J=13.8 Hz, 1H), 1.51 (m, 2H), 1.34 (s, 9H); (KBr) 3293, 2931, 1689, 1645 cm^{-1}; HRMS m/z 629.2943 (calc. of monoisotopic mass for $C_{32}H_{43}N_3O_{10}$ gives 629.2948).

Example 12-7: 5-[(2S)-3-(Benzylamino)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenyl-propa-noyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and benzylamine (31 μL) according to Method A to give a material which was re-purified by reversed phase C-18 HPLC in absence of trifluoroacetic acid to give the title compund (29 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.78 (s, 1H), 7.36 (dd, J=2.0 Hz, J=8.6 Hz, 1H), 7.30-7.13 (m, 10H), 6.96 (d, J=8.5 Hz, 1H), 4.79 (s, 2H), 4.58 (t, J=6.9 Hz, 1H), 3.11-2.94 (m, 4H), 2.76 (dd, J=10 Hz, J=13.4 Hz, 1H), 1.33 (s, 9H); IR (KBr) 3304, 2979, 1694, 1640 cm^{-1}; HRMS m/z 619.2511 (calc. of monoisotopic mass for $C_{33}H_{37}N_3O_9$ gives 619.2530).

Example 12-8: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(6-hydroxyhexyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 6-amino-1-hexanol (34 mg) according to Method A to give the title compound (64 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.79 (s, 1H), 7.43 (d, J=8.1 Hz, 1H), 7.27-7.18 (m, 5H), 7.02 (dd, J=7.0 Hz, J=8.5 Hz, 1H), 4.80 (s, 2H), 4.57 (m, 1H), 4.25 (dd, J=4.8 Hz, J=9.5 Hz, 1H), 3.77 (m, 1H), 2.74 (dd, J=10.2 Hz, J=13.2 Hz, 1H), 1.34 (s, 9H); IR (KBr) 3291, 2932, 1691, 1647 cm^{-1}; HRMS m/z 629.2948 (calc. of monoisotopic mass for $C_{32}H_{43}N_3O_{10}$ gives 629.2948).

Example 12-9: 5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[(1R)-1-(hydroxymethyl)-3-methylbutyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and D-leucinol (37 uL) according to Method A to give the title compund (51 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.79 (s, 1H), 7.44 (d, J=8.1 Hz, 1H), 7.29-7.18 (m, 5H), 7.04 (d, J=8.5 Hz, 1H), 4.80 (s, 2H), 4.55 (t, J=7.0 Hz, 1H), 4.25 (dd, J=4.8 Hz, J=9.5 Hz, 1H), 3.86 (m, 1H), 2.75 (dd, J=9.5 Hz, J=13.5 Hz, 1H), 1.35 (s, 9H), 0.82 (m, 6H); IR (KBr) 3312, 2958, 1639 cm^{-1}; HRMS m/z 629.2926 (calc. of monoisotopic mass for $C_{32}H_{43}N_3O_{10}$ gives 629.2948).

Example 12-10: 5-[(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-(phenethylamino)propyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and phenetylamine (38 uL) according to Method A to give the title compound (57 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.36 (dd, J=1.9 Hz, J=8.3 Hz, 1H), 7.28-7.15 (m, 10H), 7.00 (d, J=8.7 Hz, 1H), 4.79 (s, 2H), 4.50 (t, J=6.8 Hz, 1H),), 4.25 (dd, J=5.1 Hz, J=9.4 Hz, 1H), 3.40 (m, 1H), 3.02 (m 2H), 2.90 (dd, J=7.7 Hz, J=13.6 Hz, 1H), 1.36 (s, 9H); (KBr) 3297, 2979, 1728, 1688, 1645 cm^{-1}; HRMS m/z 633.2660 (calc. of monoisotopic mass for $C_{34}H_{39}N_3O_9$ gives 633.2686).

Example 12-11: Disodium 5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(5-hydroxypentyl)amino]-3-oxopropyl}-2-(2-oxido-2-oxoethoxy)benzoate

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 5-amino-1-pentanol (31 mg) according to Method A to give a material which was re-purified by reversed phase C-18 HPLC in absence of trifluoroacetic acid and then passed

through a column with Dowex Na+. After lyophilizing, the title compound (34 mg) was obtained. ^{1}H-NMR (400 MHz, CD_3OD) d 7.56 (s, 1H), 7.30-7.17 (m, 6H), 7.04 (d, J=8.5 Hz, 1H), 4.57-4.50 (m, 3H), 4.24 (dd, J=5.0 Hz, J=9.7 Hz, 1H), 3.52 (t, J=13.2 Hz, 2H), 3.14 (m, 1H), 3.07-2.92 (m, 4H), 2.72 (dd, J=9.8 Hz, J=13.6 Hz, 1H), 1.50 (m, 2H), 1.35 (s, 9H), 1.28 (m, 2H); (KBr) 3318, 2934, 1686, 1647 cm^{-1}; HRMS m/z 615.2821 (calc. of monoisotopic mass for $C_{31}H_{41}N_3O_{10}$ gives 615.2792).

Example 12-12: 5-((2R)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[3-(2-oxo-1-pyrrolidinyl)propyl]amino}propyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and N-(3'-aminopropyl)-2-pyrrolidinone (42 mg, 0.29 mmol) according to Method C with HPLC purification to give the title compound (26 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 1.35 (s, 9H) 1.6 (m, 2H) 2.03 (m, 2H) 2.37 (t, 2H) 2.76 (m, 1H) 2.92-3.10 (m, 5H) 3.14 (t, 2H) 3.42 (t, 2H) 4.25 (m, 1H) 4.5 (m, 1H) 4.78 (s, 2H) 7.05 (d, 1H) 7.23 (dd, 5H) 7.42 (d, 1H) 7.72 (s, 1H); HR-MS m/z 654.2880 (calc. Of monoisotopic mass for $C_{33}H_{42}N_4O_{10}$ gives 654.2901).

Example 12-13: 5-((2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[2-(dimethylamino)ethyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and N,N-dimethylenediamine (26 mg) according to Method B to give the title compound (7.2 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.50 (s, 1H), 7.35 (m, 1H), 7.29-7.20 (m, 5H), 7.13 (d, J=8.5 Hz, 1H), 4.69 (s, 2H), 4.39 (t, J=7.3 Hz, 1H), 4.29 (dd, J=5.3 Hz, J=9.2 Hz, 1H), 3.37 (m, 2H), 3.07 (dd, J=5.1 Hz, J=13.9 Hz, 1H), 2.99 (m, 4H), 2.85 (s, 6H), 2.79 (dd, J=9.0 Hz, J=13.6 Hz, 1H), 1.36 (s, 9H); HRMS m/z 600.2774 (calc. of monoisotopic mass for $C_{30}H_{40}N_4O_9$ gives 600.2795).

Example 12-14: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-pyridinylmethyl)amino]propyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 3-(aminomethyl)pyridine (31 mg) according to Method B to give the title compound (14 mg). HRMS m/z 620.2471 (calc. of monoisotopic mass for $C_{32}H_{36}N_4O_9$ gives 620.2482).

Example 12-15: 5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[3-(isopropylamino)propyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and N-isopropyl-1,3-propanediamine (34 mg) according to Method B to give the title compound (26 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.46 (d, J=2.2 Hz, 1H), 7.36 (dd, J=2.2 Hz, J=6.2 Hz, 1H), 7.29-7.20 (m, 5H), 7.08 (d, J=8.4 Hz, 1H), 4.68 (s, 2H), 4.44 (dd, J=5.7 Hz, J=9.9 Hz, 1H), 4.30 (dd, J=5.5 Hz, J=9.2 Hz, 1H), 3.27 (m, 2H), 3.06 (m, 2H), 2.89 (dd, J=10.1 Hz, J=13.0 Hz, 1H), 2.80 (m, 2H), 2.65 (m, 2H), 1.30 (dd, J=2.9 Hz, J=6.6 Hz); IR (KBr) cm^{-1}; HRMS m/z 628.3082 (calc. of monoisotopic mass for $C_{32}H_{44}N_4O_9$ gives 628.3108).

Example 12-16: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-isopropoxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 3-isopropoxypropylamine (34 mg) according to Method B to give the title compound (34 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.40 (d, J=8.3Hz, 1H), 7.28-7.17 (m, 5H), 7.03 (d, J=8.6 Hz, 1H), 4.80 (s, 2H), 4.50 (m, 1H), 4.24 (dd, J=5.1 Hz, J=9.3 Hz, 1H), 3.54 (t, J=6.1 Hz, 1H), 3.35 (m, 2H), 3.23 (m, 1H), 3.14 (m, 1H), 3.08-2.91 (m, 3H), 2.75 (dd, J=9.6 Hz, J=13.5 Hz, 1H), 1.63 (m, 2H), 1.35 (s, 9H), 1.12 (dd, J=2.0 Hz, J=6.1 Hz); IR (KBr) cm^{-1}; HRMS m/z 629.2946 (calc. of monoisotopic mass for $C_{32}H_{43}N_3O_{10}$ gives 629.2948).

Example 12-17: **5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[2-(2-pyridinyl)ethyl]amino}propyl)-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 2-(2-aminoethyl)pyridine (35 mg) according to Method B to give the title compound (56 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 8.52 (d, J=4.6 Hz, 1H), 7.97 (m, 1H), 7.69 (d, J=2.0 Hz, 1H), 7.46-7.17 (m, 8H), 7.03 (d, J=8.6 Hz, 1H), 4.78 (s, 2H), 4.46 (m, 1H), 4.23 (dd, J=5.2 Hz, J=9.4 Hz, 1H), 3.41 (m, 1H), 2.74 (dd, J=8.9 Hz, J=13.6 Hz, 1H), 1.35 (s, 9H); HRMS m/z 634.2651 (calc. of monoisotopic mass for $C_{33}H_{38}N_4O_9$ gives 634.2639).

Example 12-18: **5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[2-(1-piperazinyl)ethyl]amino}propyl)-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and N-2-aminoethyl)piperazine (37 mg) according to Method B to give the title compound (5.8 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.58 (s, 1H), 7.37 (dd, J=2.0 Hz, J=8.4 Hz, 1H), 7.26-7.18 (m, 5H), 7.13 (d, J=8.5 Hz, 1H), 4.68 (s, 2H), 4.50 (t, J=7.3 Hz, 1H), 4.28 (dd, J=5.3 Hz, J=9.0 Hz, 1H), 3.68 (m, 1H), 3.56 (m, 1H), 2.80 (dd, J=9.3 Hz, J=13.2 Hz, 1H), 2.37 (m, 1H), 1.37 (s, 9H); HRMS m/z 641.3032 (calc. of monoisotopic mass for $C_{32}H_{43}N_5O_9$ gives 641.3061).

Example 12-19: **5-[(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-({2-[(2-hydroxypropyl)amino]ethyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and N-(2-hydroxypropyl)ethylenediamine (34 mg) according to Method B to give the title compound (26 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.56 (d, J=2.4 Hz, 1H), 7.32 (d, J=8.8 Hz, 1H), 7.28-7.17 (m, 5H), 7.05 (d, J=8.5 Hz, 1H), 4.37 (m, 1H), 4.27 (dd, J=5.2 Hz, J=8.9 Hz, 1H), 1.35 (s, 9H), 1.22 (dd, J=1.8 Hz, J=6.2 Hz, 3H); HRMS m/z 630.2883 (calc. of monoisotopic mass for $C_{31}H_{42}N_4O_{10}$ gives 630.2901).

Example 12-20: **5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(4-methoxybenzyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 4-methoxybenzylamine (40 mg) according to Method B to give the title compound (33 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.75 (s, 1H), 7.34 (dd, 1H), 7.26-7.18 (m, 5H), 7.05 (d, J=8.6 Hz, 1H), 6.94 (d, J=8.6 Hz, 2H), 6.82 (m, 2H), 4.77 (s, 2H), 4.56 (m, 1H), 4.15 (dd, J=5.1 Hz, J=14.7 Hz, 1H), 3.76 (s, 3H), 3.08-2.94 (m, 3H), 2.76 (dd, J=9.6 Hz, J=13.7 Hz, 1H), 1.33 (s, 9H); HRMS m/z 649.2615 (calc. of monoisotopic mass for $C_{34}H_{39}N_3O_{10}$ gives 649.2635).

Example 12-21: **5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-hydroxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 3-amino-1-propanol (18 ul) according to Method A to give material was re-purified by reversed phase HPLC in absence of trifluoroacetic acid to give the title compound (11 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.84 (s, 1H), 7.39 (d, J=8.3 Hz, 1H), 7.27-7.17 (m, 5H), 7.04 (d, J=8.5 Hz, 1H), 4.79 (s, 2H), 4.51 (m, 1H), 4.23 (dd, J=5.2 Hz, J=9.3 Hz, 1H), 3.25 (m, 1H), 3.15 (m, 1H), 2.75 (m, 1H), 1.62 (m, 2H), 1.36 (s, 9H); HRMS m/z 587.2493 (calc. of monoisotopic mass for $C_{29}H_{37}N_3O_{10}$ gives 587.2479).

Example 12-22: **5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[2-(3-hydroxy-3-phenylpropanoyl)hydrazino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and 3-phenylhydracrylic acid hydrazide (39 mg, 0.22 mmol) according to Method C with HPLC purification to give the title compound (58 mg) as a diasteromeric mixture. ^{1}H-NMR (400 MHz, CD_3OD) d 7.77 (1H), 5.11 (dd, J=4.6 Hz, J=8.6 Hz, 1H), 4.78 (2H), 4.70 (m, 1H), 4.24 (dd, J=5.0 Hz, J=9.3 Hz, 1H), 1.34 (s, 9H); IR (KBr) 3274,

1681, 1652, 1608 cm^{-1}; HRMS m/z 692.2670 (calc. of monoisotopic mass for $C_{35}H_{40}N_4O_{11}$ gives 692.2694).

Example 12-23: 5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{2-[(2-hydroxy[1,1'-biphenyl]-3-yl)carbonyl]hydrazino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (93 mg, 0.17 mmol) and 3-phenylsalicylic acid hydrazide (45 mg, 0.20 mmol) according to Method C with HPLC purification to give the title compound (30 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 4.80 (s, 2H), 4.27 (dd, J=4.9 Hz, J=9.8 Hz, 1H), 3.04 (m, 1H), 2.94 (m, 1H), 2.72 (dd, J=9.3 Hz, J=13.7 Hz, 1H), 1.34 (s, 9H); IR (KBr) 3280, 1694, 1653 cm^{-1}; HRMS m/z 740.2666 (calc. of monoisotopic mass for $C_{39}H_{40}N_4O_{11}$ gives 740.2694).

Example 12-24: 5-[(2S)-3-{2-[2-(Benzoylamino)acetyl]hydrazino}-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and hippuric acid hydrazide (42 mg, 0.22 mmol) according to Method C with HPLC purification to give the title compound (24 mg). IR (KBr) 3274, 1652, 1616 cm^{-1}; HRMS m/z 705.2640 (calc. of monoisotopic mass for $C_{35}H_{39}N_5O_{11}$ gives 705.2646).

Example 12-25: 5-[(2S)-3-({2-[5-(Benzyloxy)-1H-indol-3-yl]-1-methylethyl}amino)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (68 mg, 0.12 mmol) and 3-(2-aminopropyl)-5-(benzyloxy)-indole hydrochloride (46 mg, 0.15 mmol) according to Method C with HPLC purification to give the title compound (32 mg) as a diasteromeric mixture. IR (KBr) 3409, 1681, 1652 cm^{-1}; HRMS m/z 792.3360 (calc. of monoisotopic mass for $C_{44}H_{48}N_4O_{10}$ gives 792.3370).

Example 12-26: **5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3,3-diphenylpropoxy)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (85 mg, 0.15 mmol) and 3,3-diphenylpropoxyamine hydrochloride (48 mg, 0.18 mmol) according to Method C with HPLC purification to give the title compound (29 mg). 7.75 (s, 1H), 7.33 (d, J=9.5 Hz, 1H), 6.87 (d, J=8.3 Hz, 1H), 4.71 (s, 2H), 4.39 (dd, 1H), 4.25 (m, 1H), 4.11 (t, J=8.0 Hz, 1H), 3.57 (m, 2H), 3.01 (m, 2H), 2.93 (m, 1H), 2.75 (m, 1H), 2.24 (m, 2H), 1.35 (s, 9H); IR (KBr) 3274, 2978, 1684, 1651 cm^{-1}; HRMS m/z 739.3126 (calc. of monoisotopic mass for $C_{41}H_{45}N_3O_{10}$ gives 739.3105).

Example 12-27: **5-[(2S)-3-{[3-(Benzylanilino)-2-hydroxypropyl]amino}-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (85 mg, 0.15 mmol) and 1-amino-3-(N-benzylanilino)-2-propanol (47 mg, 0.18 mmol) according to Method C with HPLC purification to the title compound (23 mg) as a diasteromeric mixture. IR (KBr) 3414, 1654 cm^{-1}; HRMS m/z 768.3382 (calc. of monoisotopic mass for $C_{42}H_{48}N_4O_{10}$ gives 768.3370).

Example 12-28: **5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylpropoxy)amino]propyl}-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and 3-phenylpropoxyamine (41 mg, 0.22 mmol) according to Method C with HPLC purification to give the title compound (53 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.57 (s, 1H), 6.94 (d, J=8.3 Hz, 1H), 4.28 (m, 1H), 3.65 (m, 2H), 3.04 (dd, J=4.9 Hz, J=13.9 Hz, 1H), 2.97 (m, 1H), 2.73 (dd, J=9.6 Hz, J=13.8 Hz, 1H), 2.65 (t, J=7.7 Hz, 2H), 1.78 (m, 2H), 1.37 (s, 3H), 1.36 (s, 6H); IR (KBr) 3293, 2949, 1681, 1651 cm^{-1}; HRMS m/z 663.2806 (calc. of monoisotopic mass for $C_{35}H_{41}N_3O_{10}$ gives 663.2792).

Example 12-29: 5-((2S)-2-({(2R)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[2-(1-pyrrolidinyl)ethyl]amino}propyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and N-(2-aminoethyl)pyrrolidinone (33 mg, 0.29 mmol) according to Method C with HPLC purification to give the title compound (10 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 1.36 (s, 9H) 2.05 (s, 4H) 2.68-3.20 (m, 8H) 3.39 (m, 4H) 4.28 (m, 1H) 4.39 (m, 1H) 4.69 (s, 2H) 7.05-7.40 (m, 7H) 7.52 (s, 1H); HRMS m/z 626.2929 (calc. of monoisotopic mass for $C_{32}H_{42}N_4O_9$ gives 626.2952).

Example 12-30: 5-{(2S)-2-({(2R)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3,4-dimethoxyphenethyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and 3,4-dimethoxyphenethylamine (52 mg, 0.29 mmol) according to Method C with HPLC purification to give the title compound (12 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 1.38 (s, 9H) 2.68 (t, 2H) 2.72-3.09 (m, 4H) 3.29-3.44 (m, 2H) 3.80 (s, 3H) 3.85 (s, 3H) 4.25 (m, 1H) 4.52 (m, 1H) 4.79 (s, 2H) 6.74 (d, 1H) 6.84 (s, 1H) 6.87 (d, 1H) 7.06 (d, 1H) 7.17-7.38 (m, 6H) 7.73 (s, 1H); HRMS m/z 693.2904 (calc of monoisotopic mass for $C_{36}H_{43}N_3O_{11}$ gives 693.2898).

Example 12-31: 5-((2S)-2-({(2R)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[2-hydroxy-2-(1-phenyl-1H-indol-3-yl)ethyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid(49 mg, 0.08 mmol) and N-phenyl-3-(1-hydroxy-2-aminoethyl)indole malonate (45 mg, 0.14 mmol) according to Method C with HPLC purification to give the title compound (13 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 1.30-1.31 (d, 9H) 2.65 (m, 1H) 2.80-3.06 (m, 3H) 3.45 (m, 1H)

3.72 (m, 1H) 4.19 (m, 1H) 4.52 (m, 1H) 4.67 (d, 2H) 5.03 (m, 1H) 7.0-7.8 (m, 18H); HRMS m/z 764.3073 (calc. of monoisotopic mass for $C_{42}H_{44}N_4O_{10}$ gives 764.3057).

Example 12-32: 5-[(2S)-2-({(2R)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-({5-[(phenylsulfonyl)amino]pentyl}amino)propyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (45 mg) and N-(5-aminopentyl)-benzenesulphonamide malonate (45 mg, 0.08 mmol) according to Method C with HPLC purification to give the title compound (4.2 mg, 0.13 mmol). ^{1}H-NMR (400 MHz, CD_3OD) δ 0.97 (m, 1H) 1.16-1.49 (m, 16H) 2.73-3.16 (m, 6H) 4.26 (m, 1H) 4.50 (m, 1H) 4.68 (s, 2H) 7.09-7.9 (m, 13 H); HRMS 754.2859 (calc of monoisotopic mass for $C_{37}H_{46}N_4O_{11}S$ gives 754.2884).

Example 12-33: 5-[(2S)-3-{2-[2-(Benzoylamino)-3-methylbutanoyl]hydrazino}-2-({(2R)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (66 mg, 0.12 mmol) and N-benzoylvaline hydrazide (45 mg, 0.19 mmol) according to Method C with HPLC purification to give the title compound (3.5 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 1.10 (m, 6H) 1.35 (s, 9H) 1.43 (m, 1H) 2.25 (m, 1H) 2.68 (m, 1H) 2.90 (m, 2H) 3.51 (m, 1H) 4.24 (m, 1H) 4.51 (m,1H) 4.70 (m, 2H) 7.02-8.0 (m, 13H); HRMS m/z 747.3098 (calc of monoisotopic mass for $C_{38}H_{45}N_5O_{11}$ gives 747.3116).

Example 12-34: 5-[2-({2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-(dipentylamino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and dipentylamine (46 mg, 0.29 mmol) according to Method C with HPLC purification to give the title compound (64 mg). ^{1}H-NMR (400 MHz, CD_3OD) δ 0.90 (m, 6H) 1.14-1.53 (m, 21H) 2.65-2.82 (m, 1H) 2.86-3.38 (m, 7H) 4.30 (m, 1H) 4.80 (d, 2H) 4.94 (m,

1H) 7.02 (m, 1H) 7.21 (m, 5H) 7.35-7.45 (dd, 1H) 7.76 (dd, 1H); HRMS m/z 669.3634 (calc. of monoisotopic mass for $C_{36}H_{51}N_3O_9$ gives 669.3625); mp 87-90 °C.

Example 12-35: 5-{(2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(4-hydroxybutyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid and 4-amino-1-butanol (21 ul) according to Method A to give a material which was re-purified by reversed phase C-18 HPLC in absence of trifluoroacetic acid to give the title compound (19 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.75 (s, 1H), 7.40 (d, J=8.3 Hz, 1H), 7.28-7.18 (m, 5H), 7.04 (d, J=8.8 Hz, 1H), 4.79 (s, 2H), 4.51 (m, 1H), 4.24 (dd, J=5.2 Hz, J=9.2 Hz, 1H), 3.52 (m, 1H), 3.18 (m, 1H), 3.09-2.92 (m, 4H), 2.75 (m, 1H), 1.45 (m, 4H), 1.36 (s, 9H); HRMS m/z 601.2616 (calc. of monoisotopic mass for $C_{30}H_{39}N_3O_{10}$ gives 601.2635).

Example 12-36: 5-((2S)-2-({(2S)-2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[2-(2-fluoro[1,1'-biphenyl]-4-yl)propyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (79 mg, 0.14 mmol) and 2-fluoro-β-methyl-4-biphenylethylamine hydrochloride (45 mg, 0.17 mmol) according to Method C to give the title compound (44 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.75 (s, 1H), 4.78 (s, 1H), 4.57 (s, 1H), 4.51 (m, 1H), 4.22 (m, 1H), 3.52 (m, 1H), 3.41 (m, 1H), 3.22 (m, 1H), 3.06-2.85 (m, 4H), 2.72 (m, 1H), 1.35 (s, 9H), 1.20 (dd, J=7.0 Hz, J=15.7 Hz, 4H); HRMS m/z 741.3094 (calc. of monoisotopic mass for $C_{41}H_{44}FN_3O_9$ gives 741.3062).

Example 12-37: 5-((2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[2-hydroxy-2-(3-phenoxyphenyl)ethyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (96 mg, 0.16 mmol) and 2-amino-1-(3-phenoxyphenyl)-1-etanol (45 mg, 0.20 mmol)

according to Method C with HPLC purification to give the title compound (25 mg) as a diasteromeric mixture. ^{1}H-NMR (400 MHz, CD_3OD) d 7.59 (d, J=1.7 Hz, 1H), 6.87 (dd, J=1.2 Hz, J=8.3 Hz, 1H), 4.66 (m, 3H), 4.55 (t, J=7.0 Hz, 1H), 4.23 (m, 1H), 3.02 (m, 2H), 3.52 (m, 1H), 2.90 (m, 1H), 2.69 (m, 1H), 1.34 (s, 9H); HRMS m/z 741.2925 (calc. of monoisotopic mass for $C_{40}H_{43}N_3O_{11}$ gives 741.2898).

Example 12-38: 5-((2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-{[(4-hydroxy-2-phenyl-3,4-dihydro-2H-chromen-4-yl)methyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (82 mg, 0.15 mmol) and 4-(aminomethyl)-2-phenyl-4-chromanol (45 mg, 0.18 mmol) according to Method C with HPLC purification to give the title compound (15 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.64 (s, 1H), 6.84 (dd, J=1.0 Hz, J=8.3 Hz, 1H), 5.33 (d, J=12.0 Hz, 1H), 4.64 (s, 2H), 4.63 (m, 1H), 4.28 (m, 1H), 3.95 (m, 1H), 3.19 (m, 1H), 1.35 (s, 3H), 1.32 (s, 6H); HRMS m/z 767.3084 (calc. of monoisotopic mass for $C_{42}H_{45}N_3O_{11}$ gives 767.3054).

Example 12-39: 5-[(2S)-3-({2-[2-(benzyloxy)-5-chlorophenyl]-2-hydroxyethyl}amino)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (75 mg, 0.13 mmol) and 2-amino-1-[2-(benzyloxy)-5-chlorophenyl]-1-ethanol (45 mg, 0.16 mmol) according to Method C to give the title compound (66 mg) as a diasteromeric mixture. ^{1}H-NMR (400 MHz, CD_3OD) d 4.77 (s, 1H), 4.75 (s, 1H), 4.55 (m, 1H), 4.22 (m, 1H), 1.33-1.32 (9H); HRMS m/z 789.2713 (calc. of monoisotopic mass for $C_{41}H_{44}ClN_3O_{11}$ gives 789.2664).

Example 12-40: 5-[(2S)-3-{[2-(1-benzyl-1H-indol-3-yl)ethyl]amino}-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic

acid (73 mg, 0.13 mmol) and 2-(1-benzyl-1H-indol-3-yl)ethylamine hydrochloride (45 mg, 0.16 mmol) according to Method C to give the title compound (48 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.56 (d, J=7.6 Hz, 1H), 6.81 (d, J=8.5 Hz, 1H), 5.28 (s, 2H), 4.69 (s, 2H), 4.48 (m, 1H), 4.22 (dd, J=5.2 Hz, J=9.2 Hz, 1H), 3.52 (m, 1H), 3.38 (m, 1H), 2.98 (m, 2H), 2.86 (m, 3H), 2.72 (dd, J=9.3 Hz, J=13.8 Hz, 1H), 1.33 (s, 9H); HRMS m/z 762.3292 (calc. of monoisotopic mass for $C_{43}H_{46}N_4O_9$ gives 762.3265).

Example 12-41: 5-{2-({2-[(tert-Butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[methyl(pentyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and N-methylamylamine (29 mg, 0.29 mmol) according to Method C with HPLC purification to give the title compound (33 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 7.5-7.15 (m, 6H), 7.04 (d, 1H), 5.02 (m, 1H), 4.81 (s, 2H), 4.28 (m, 1H), 3.25-2.7 (m, 9H), 1.10-1.5 (m, 15H), 0.89 (t, 3H); HRMS m/z 613.2982 (calc. of monoisotopic mass for $C_{32}H_{43}N_3O_9$ gives 613.2999).

Example 12-42: 5-[(2S)-3-{[2-(Benzylsulfanyl)ethyl]amino}-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (100 mg, 0.18 mmol) and 2-(benzylsulfanyl)-1-ethanamine hydrochloride (44 mg, 0.22 mmol) according to Method C with HPLC purification to give the title compound (15 mg). ^{1}H-NMR (400 MHz, CD_3OD) d 7.76 (s, 1H), 6.97 (d, J=8.6 Hz, 1H), 4.77 (s, 2H), 4.51 (m, 1H), 4.24 (dd, J=5.1 Hz, J=9.3 Hz, 1H), 3.71 (s, 2H), 3.19 (m, 1H), 2.74 (m, 1H), 2.41 (m, 2H), 1.35 (s, 9H); HRMS m/z 679.2542 (calc. of monoisotopic mass for $C_{34}H_{41}N_3O_9S$ gives 679.2564).

Example 12-43: 5-[(2S)-3-[([1,1'-Biphenyl]-4-ylmethoxy)amino]-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (91 mg, 0.16 mmol) and 4-[(aminooxy)methyl]-1,1'-biphenyl hydrochloride (46 mg, 0.20 mmol) according to Method C with HPLC purification to give the title compound (47 mg). ^{1}H-

NMR (400 MHz, CD_3OD-Me_2SO-d6) d 7.74-7.16 (17H), 4.84 (1H), 4.76 (1H), 4.64 (s, 2H), 4.32 (m, 1H), 3.03 (m,3H), 1.41 (s, 9H); IR (KBr) 3272, 2978, 1681, 1652 cm^{-1}; HRMS m/z 711.2831 (calc. of monoisotopic mass for $C_{39}H_{41}N_3O_{10}$ gives 711.2792).

Example 12-44: **5-[(2S)-3-{[2-(Benzylamino)-2-phenylethyl]amino}-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (70 mg, 0.13 mmol) and N^1-benzyl-1-phenyl-1,2-ethandiamine dihydrochloride (45 mg, 0.15 mmol) according to Method C with HPLC purification to give the title compound (11 mg) as a diastereomeric mixture. ^{1}H-NMR (400 MHz, CD_3OD) d 7.50 (1H), 7.45-7.03 (17H), 4.40 (m, 1H), 4.25 (m, 1H), 4.06 (m, 1H), 3.80 (s, 2H), 3.03 (m, 1H), 1.33 (s, 9H); HRMS m/z 738.3281 (calc. of monoisotopic mass for $C_{41}H_{46}N_4O_9$ gives 738.3265).

Example 12-45: **5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(1-methyl-3,3-diphenylpropyl)amino]-3-oxopropyl]-2-(carboxymethoxy)benzoic acid**

Synthesis was performed from (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid (88 mg, 0.16 mmol) and 1-methyl-3,3-diphenylpropylamine (45 mg, 0.19 mmol) according to Method C with HPLC purification to give the title compound (31 mg) as a diastereomeric mixture in a 2:1 ratio. HRMS m/z 737.3312 (calc. of monoisotopic mass for $C_{42}H_{47}N_3O_9$ gives 737.3329).

Preparation of starting material: **(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid**

General. All experiments were carried out under N_2-atmosphere, except the hydrogenation and carbonylation reactions. Melting points were determined in open glass capillaries on a Gallenkamp apparatus and were not corrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX 400 spectrometer at 400.1 and 100.6 MHz, respectively or on a Bruker

DRX 500 at 500 MHz and at 125.7 MHz, respectively. ^{1}H NMR and ^{13}C NMR spectra were referenced to internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Ionspray MS spectra were obtained on a Perkin Elmer API 150EX mass spectrometer. Thin-layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). Column chromatography was performed on silica using Kieselgel 60 (230-400 mesh), E. Merck. The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden.

a) Benzyl (2S)-2-amino-3-(4-hydroxy)-3-iodophenyl)propanoate hydrochloride

3-Iodo-L-tyrosine (5.0 g, 16.3 mmol) was suspended in benzyl alcohol (100 mL) and at 0 °C, thionyl chloride (20 mL) was added dropwise over a 20-min period. The temperature was raised to 80 °C and HCl (g) started to evolve. The reaction mixture became yellow turbid and turned to clear colorless after 30 min. After 8 h of heating, the mixture was stirred overnight at ambient temperature. Dry diethyl ether (150 mL) was added and the flask was stored overnight at -10 °C. The white product was collected on a glass-sintered funnel and dried (1.91 g). An additional amount of 2.65 g was obtained after the addition of i-hexane and storage at -10 °C. The combined material was taken up in 5% $NaHCO_3$ (200 mL) and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo leaving a crude yellow oil (4.00 g; 64 %). Mp (HCl salt): 187-188 °C; ^{1}H NMR (HCl salt, CD_3OD) δ 3.02 (d, J = 6.8, 2H), 4.22 (t, J = 6.8, 1H), 5.15 (q, J_1 = 15.9 , J_2 = 3.9, 2H), 6.68 (d, J = 8.3, 1H), 6.91, (dd, J_1 = 8.3, J_2 = 2.2, 1H), 7.23-7.31 (m, 5H), 7.51 (d, J = 2.2, 1H); ^{13}C NMR (HCl salt, CD_3OD) δ 36.44, 55.61, 69.60, 85.56, 116.48, 128.11, 130.14, 130.22, 130.28, 131.99, 136.49, 141.55, 158.35, 170.34; MS (Ionspray, $[M+H]^+$) m/z 396.2; Anal. Calcd. (found) for $C_{16}H_{16}INO_3 \cdot HCl$: C 44.3 (44.7) % H 4.0 (3.9) % N 3.2 (3.2) %.

b) Benzyl (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-(4-hydroxy-3-iodophenyl)propanoate

The free base of benzyl (2S)-2-amino-3-(4-hydroxy)-3-iodophenyl)propanoate hydrochloride (3.97 g, 10.0 mmol) was dissolved in dichloromethane (75 mL) and stirred at 0 °C under N_2-atmosphere. Then, EDC (1.92 g, 10.0 mmol), HOBT (1.35 g, 10.0 mmol)) and BOC-L-Phe (2.65 g, 10.0 mmol) were added simultaneously and triethylamine 1.39 mL, 10.0 mmol) was added dropwise. This reaction mixture was stirred for 15 h allowing to warm to ambient

temperature. Ethyl acetate (200 mL) was added and the organic layer was washed with 5 % HCl (2 × 200 mL). The combined aqueous phases were extracted with ethyl acetate (100 mL) after which the combined organic layers were washed with 10% $NaHCO_3$ (100 mL). Drying (Na_2SO_4), filtration and evaporation in vacuo gave an off-white foam (6.01 g, 93%). The product was purified by flash column chromatography on silica gel eluting with chloroform giving a 4.88 g (76%) of a white foam. Mp: 81.6-82.7 °C; ^{1}H NMR δ 1.39 (s, 9H), 2.89-2.98 (m, 2H), 3.03 (d, J = 6.5, 2H), 4.33 (m, 1H), 4.75 (m, 1H), 4.94 (br s, 1H), 5.10 (s, 2H), 5.60 (br s, 1H), 6.37 (d, J = 8.0, 1H), 6.73, (s, 1H), 7.17-7.39 (m, 11H); ^{13}C NMR δ 28.24, 36.52, 38.26, 53.34, 55.85, 67.36, 85.47, 115.02, 128.59, 128.66, 128.71, 128.75, 129.30, 129.58, 131.04, 134.86, 136.39, 138.79, 154.04, 170.58, 170.91; MS (Ionspray, $[M-H]^+$) m/z 643.2; Anal. Calcd. (found) for $C_{30}H_{33}IN_2O_6$: C 55.9 (56.3) % H 5.2 (5.2) % N 4.4 (4.7) %

c) Methyl 5-[(2S)-3-(benzyloxy)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-hydroxybenzoate

A mixture of benzyl (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-(4-hydroxy-3-iodophenyl)propanoate (4.43 g, 6.87 mmol), $Pd(OAc)_2$ (50 mg, 3.3 mol%) and DPPF (230 mg, 6.2 mol%) in acetonitrile (20 mL) was treated with trietylamine (1.9 mL, 13.74 mmol) and methanol (4.4 mL). A carbon monoxide atmosphere was established and the reaction mixture was heated at 70 °C (Essential! Solvent vapour displaces CO if temperature is too high) for 16 h. The darkbrown reaction mixture was directly coated on silica gel and subjected to column chromatography (3 × 20 cm) eluting with chloroform. Pure fractions were pooled giving 2.45 g (62%) off-white solid after evaporation of the eluent. Pure material can be obtained by recrystallization from abs. ethanol. ^{1}H NMR δ 1.38 (s, 9H), 2.98-3.05 (m, 4H), 3.87 (s, 3H), 4.37 (br s, 1H), 4.78 (q, J_1 = 13.2 , J_2 = 7.2, 1H), 4.99 (br s, 1H), 5.08 (s, 2H), 6.43 (d, J = 7.5, 1H), 6.76 (d, J = 8.5, 1H), 6.95 (dd, J_1 = 8.5, J_2 = 2.2, 1H), 7.16-7.37 (m, 10H) 7.46 (d, J = 2.2, 1H), 10.62 (s, 1H); ^{13}C NMR δ 28.19, 36.97, 38.19, 52.30, 53.35, 55.71, 67.28, 80.27, 112.11, 117.77, 126.20, 126.99, 128.50, 128.60, 128.66, 129.28, 130.30, 134.84, 136.45, 136.68, 155.33, 160.58, 170.20, 170.65, 170.87; MS (Ionspray, $[M-H]^+$) m/z 575.2; Anal. Calcd. (found) for $C_{32}H_{36}N_2O_8 \cdot 0.25\ H_2O$: C 66.1 (66.0) % H 6.3 (6.5) % N 4.8 (4.9) %

d) Methyl 5-[(2S)-3-(benzyloxy)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(2-methoxy-2-oxoethoxy)benzoate

A mixture of methyl 5-[(2S)-3-(benzyloxy)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-hydroxybenzoate (1.68 g, 2.91 mmol), methyl bromoacetate (0.83 uL, 3 eq.) and K_2CO_3 (activated, 1.20 g, 3 eq.) in acetone (20 mL) was heated at 50 °C overnight. TLC showed complete conversion and water (20 mL) was added. Extraction with dichloromethane (3 × 25 mL), drying (Na_2SO_4) and removal of the solvent at the rotavapor afforded 2.27 g of a yellow oil. Flash column chromatography on silica gel (2 × 20 cm) eluting with chloroform gave 1.17 g (62%) of a pure colorless oil, that solidified on standing. An additional amount (0.45 g) impure colorless oil was isolated. ^{1}H NMR δ 1.36 (s, 9H), 2.95-3.11 (m, 4H), 3.78 (s, 3H), 3.85 (s, 3H), 4.36 (br s, 1H), 4.66 (s, 2H), 4.80 (q, 1H), 5.09 (s, 2H), 5.11 (br s, 1H), 6.57 (d, 1H), 6.66 (d, 1H), 7.00 (dd, 1H), 7.17-7.37 (m, 10H) 7.48 (d, 1H); ^{13}C NMR δ 28.06, 36.69, 38.01, 52.02, 52.15, 53.12, 55.62, 66.45, 67.20, 80.05, 114.27, 120.75, 126.79, 128.34, 128.43, 128.48, 128.50, 128.90, 129.16, 132.65, 134.12, 136.49, 156.40, 165.86, 168.82, 170.48, 170.87; MS (Ionspray, $[M-H]^+$) m/z 647.4; Anal. Calcd. (found) for $C_{35}H_{40}N_2O_{10} \cdot 0.25\ H_2O$: C 64.4 (64.1) % H 6.3 (6.2) % N 4.3 (4.3) %.

e) (2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[3-(methoxycarbonyl)-4-(2-methoxy-2-oxoethoxy)phenyl]propanoic acid

Methyl 5-[(2S)-3-(benzyloxy)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxopropyl]-2-(2-methoxy-2-oxoethoxy)benzoate (0.97 g, 1.50 mmol) was hydrogenated (atmospheric pressure) in abs ethanol (30 mL) over 10% Pd/C (100 mg) for 3 h. Filtration over diatomaceous earth and evaporation in vacuo of the filtrate yielded 0.76 g (91%) of a light-grey foam. ^{1}H NMR (CD_3OD) δ 1.33 (s, 9H), 2.62-2.75 (m, 1H), 2.98-3.08 (m, 2H), 3.17-3.22 (m, 1H), 3.74 (s, 3H), 3.83 (s, 3H), 4.27 (m, 1H), 4.64 (m, 1H), 4.76 (s, 2H), 6.93 (d, 1H), 7.18-7.27 (m, 5H) 7.35 (d, 1H), 7.64 (s, 1H); ^{13}C NMR (CD_3OD) δ 28.12, 36.82, 38.71, 52.08, 54.32, 56.96, 66.52, 80.16, 114.89, 121.30, 127.15, 128.87, 129.81, 130.92, 133.06, 135.20, 138.16, 157.31, 167.67, 170.37, 173.49, 173.66; MS (Ionspray, $[M-H]^+$) m/z 557.2; Anal. Calcd. (found) for $C_{28}H_{34}N_2O_{10} \cdot 0.25\ H_2O$: C 59.7 (59.6) % H 6.2 (6.1) % N 5.0 (4.9) %

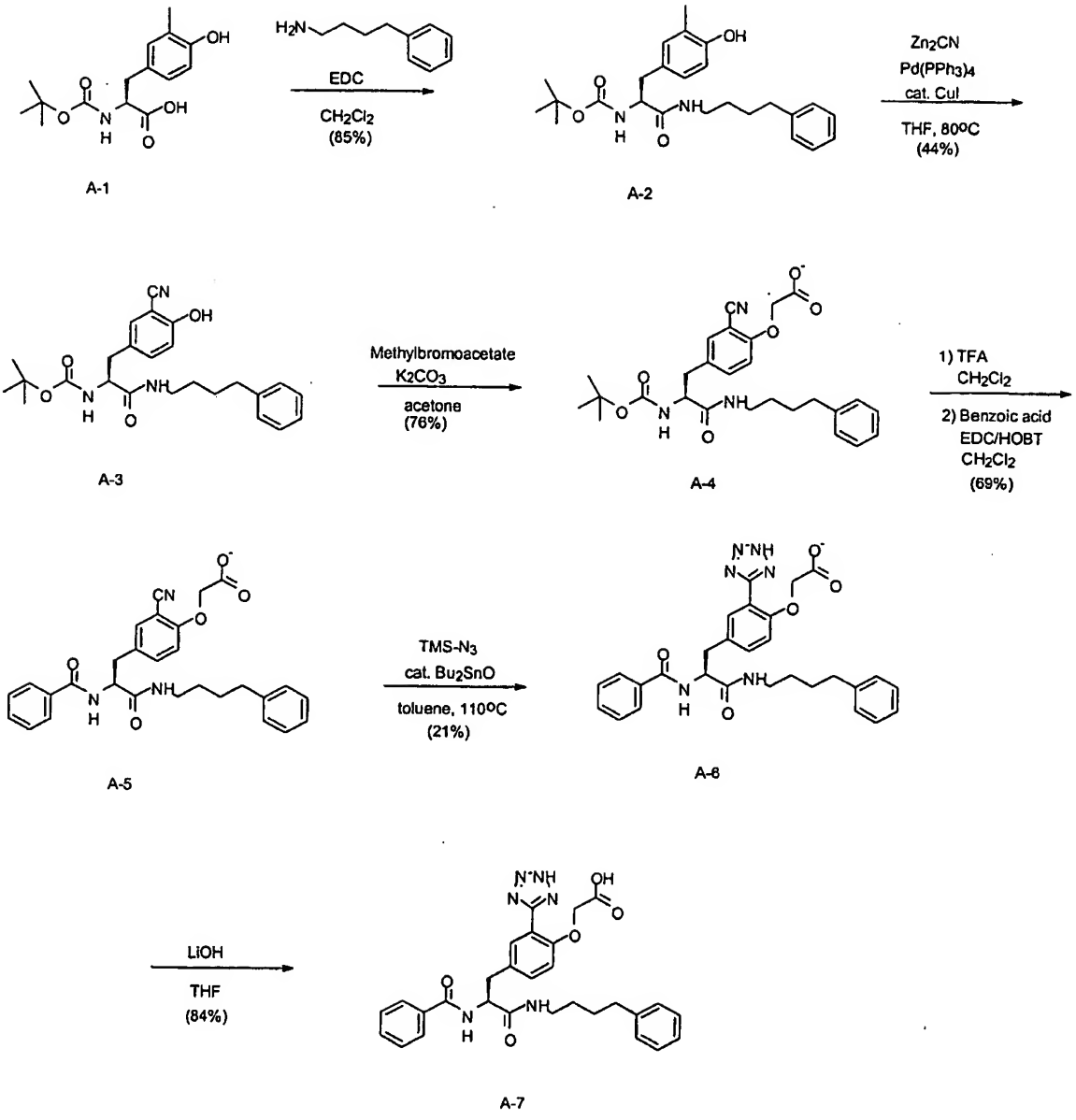
EXAMPLE 13: 2-(Carboxymethoxy)-5-[(2S)-3-oxo-3-(pentylamino)-2-({(2S)-2-[(phenoxycarbon yl)amino]-3-phenylpropanoyl}amino)propyl]benzoic acid

The title compound was prepared in analogy with the preparation of the compound of Example 6 above. MS (FAB) m/z (rel. intensity) 620 (MH+, 18), 620 (18), 231 (52), 155 (33), 154 (99), 137 (65), 109 (18), 91 (16), 57 (11), 45 (11), 43 (11). Anal. Calcd for $C_{33}H_{37}N_3O_9$: C, 63.96, H, 6.02; N, 6.78. Found: C, 64.06, H, 6.27; N, 6.53.

EXAMPLE 14: 2-(Carboxymethoxy)-5-[(2S)-2-{[(3R)-3-carboxy-4-phenylbutanoyl]amino}-3-oxo -3-(pentylamino)propyl]benzoic acid

The title compound was prepared in analogy with the preparation of the compound of Example 6 above. MS (FAB) m/z (rel. intensity) 543 (MH+, 25), 544 (9), 543 (25), 309 (15), 263 (9), 233 (10), 231 (48), 154 (99), 137 (58), 109 (15), 91 (16). MS (FAB) m/z (rel. intensity) 543 (MH+, 99), 565 (20), 544 (33), 543 (99), 238 (25), 117 (16), 107 (16), 88 (58), 43 (23), 41 (16), 23 (17). HRMS (FAB) calcd for $C_{28}H_{34}N_2O_9$+H1 543.2343, found 543.2353. Anal. Calcd for $C_{28}H_{34}N_2O_9$: C, 61.98; H, 6.32; N, 5.16. Found: C, 60.35; H, 6.35; N, 4.89.

CHART A



A-1 A-2 A-3 A-4 A-5 A-6 A-7

CHART B

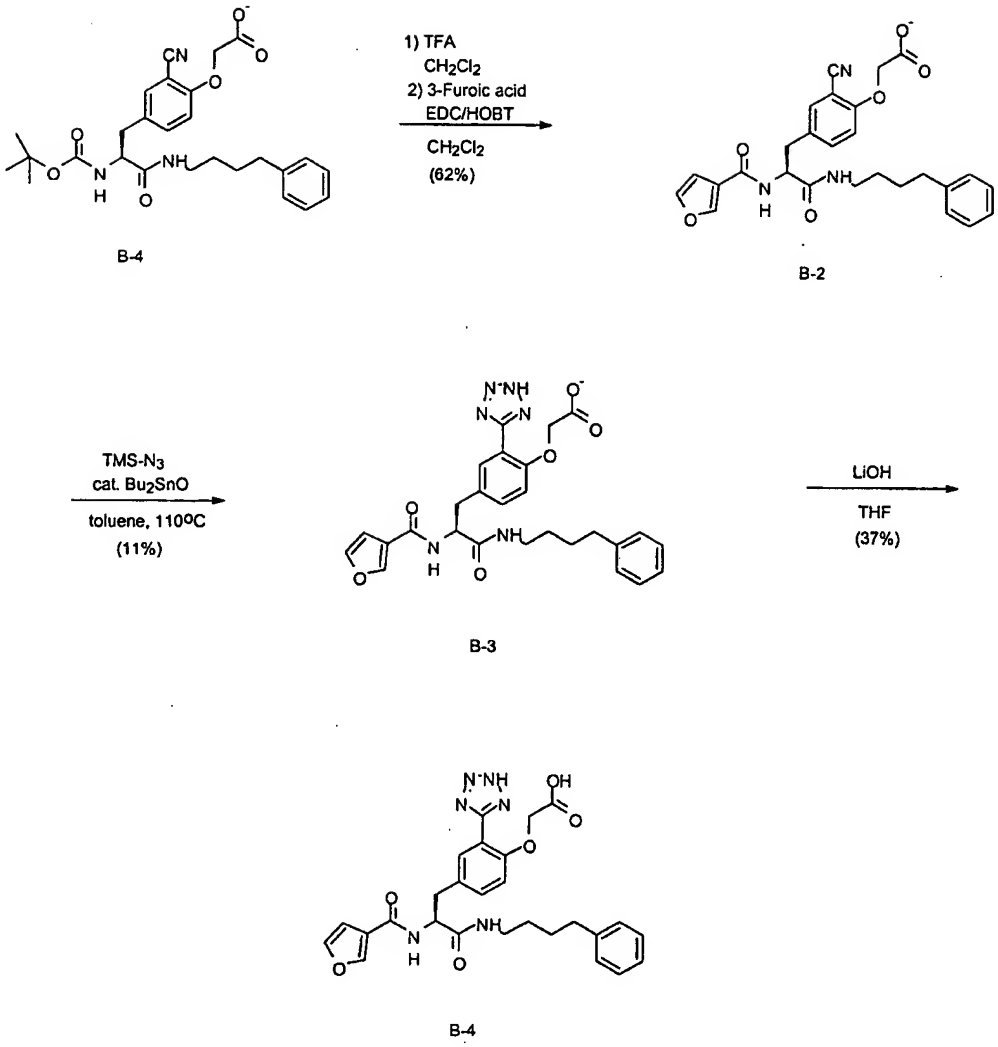
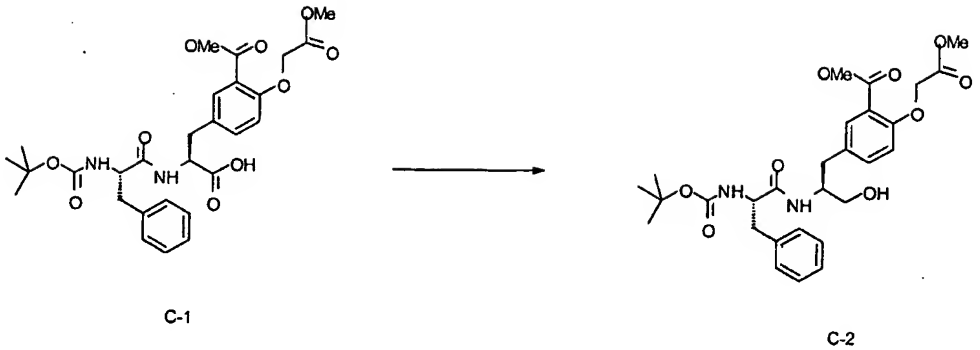
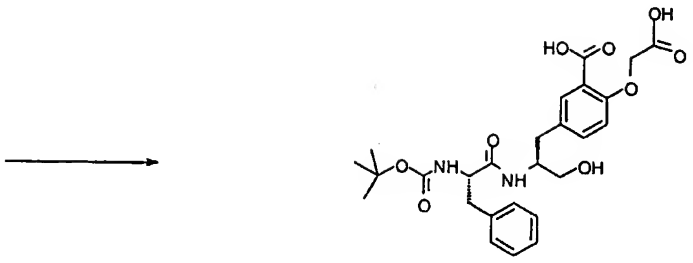

1) TFA
CH_2Cl_2
2) 3-Furoic acid
EDC/HOBT
CH_2Cl_2
(62%)
B-4
B-2
$TMS-N_3$
cat. Bu_2SnO
toluene, 110°C
(11%)
LiOH
THF
(37%)
B-3
B-4

CHART C



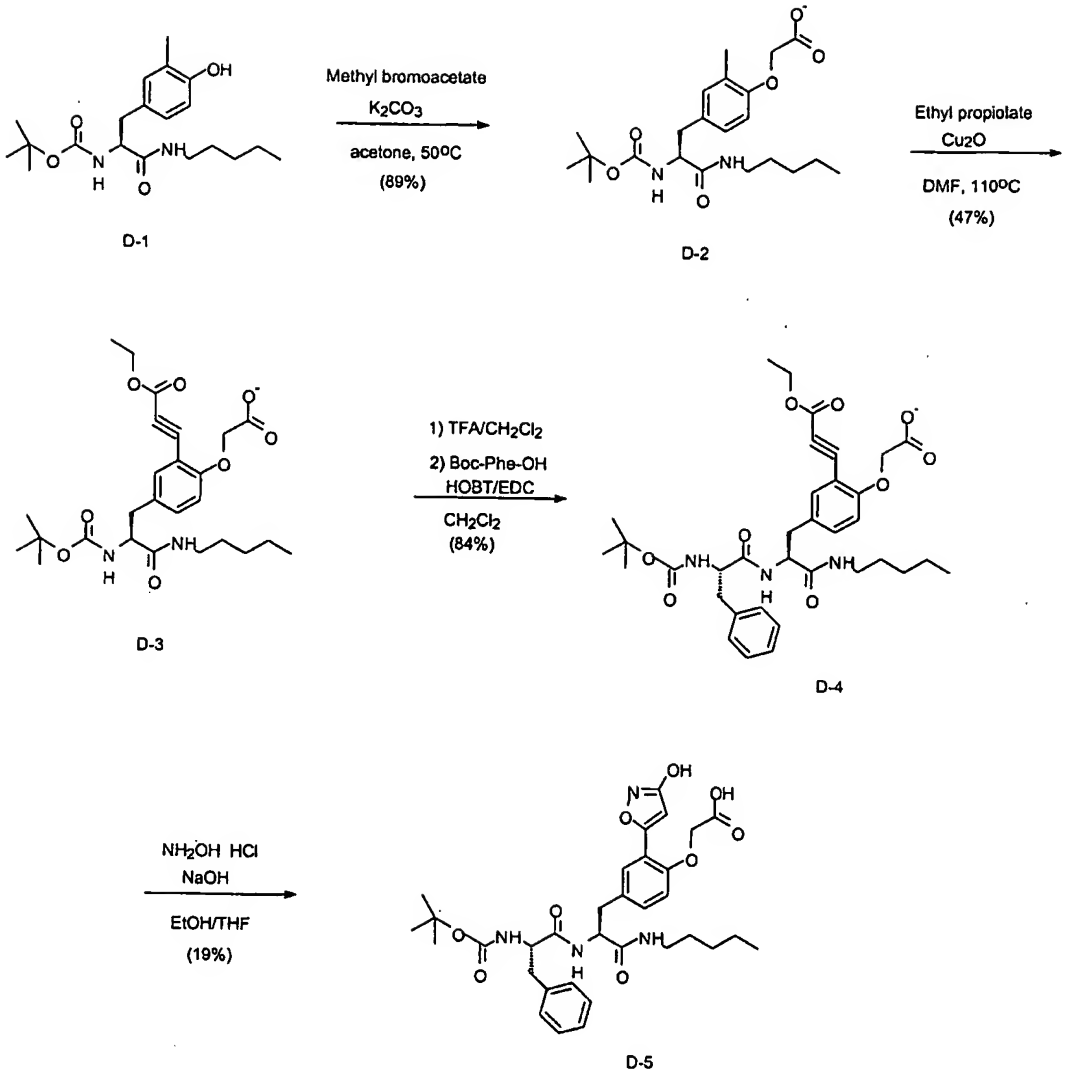
C-1

C-2



C-3

CHART D



D-1 D-2 D-3 D-4 D-5

CHART E

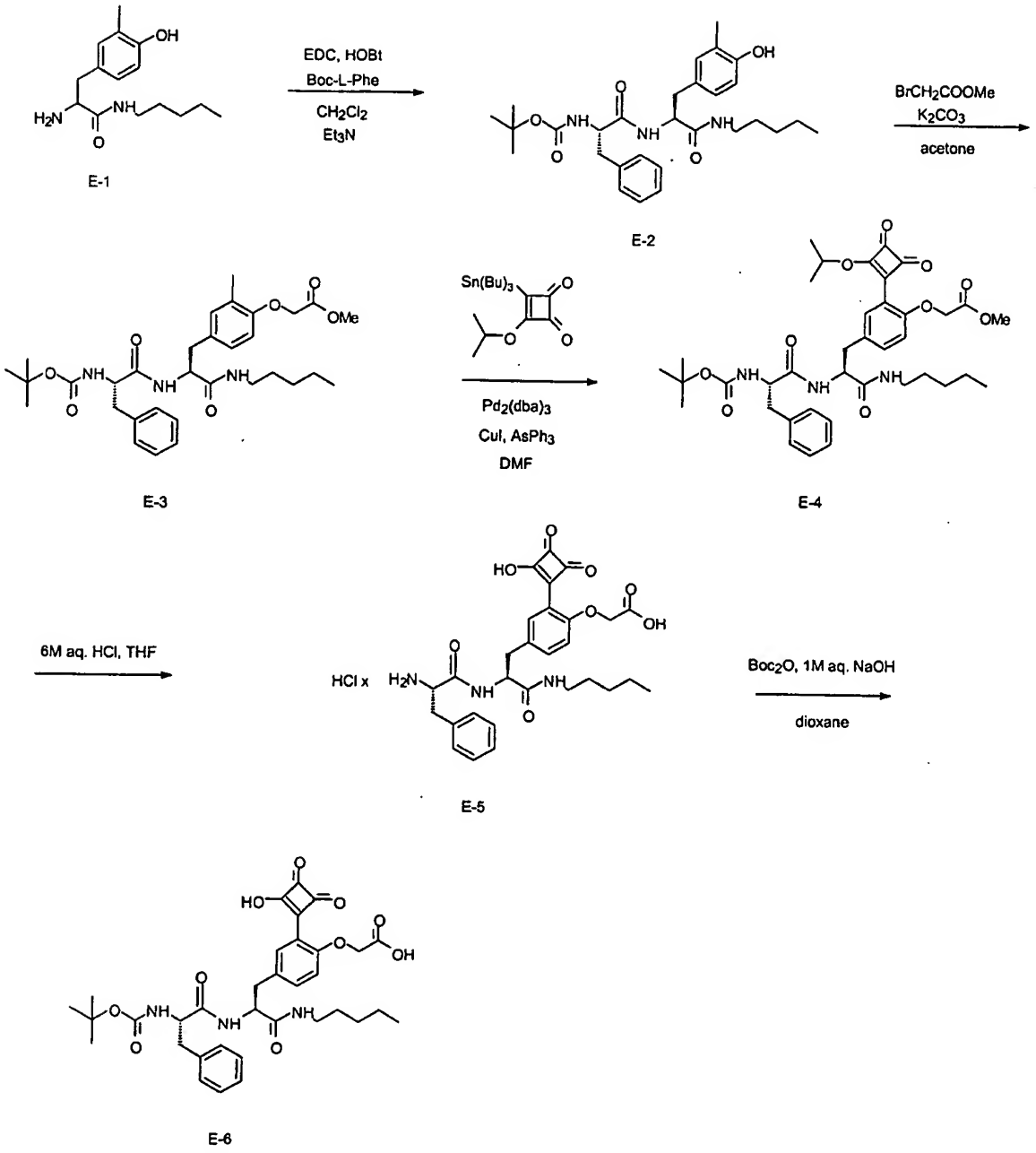
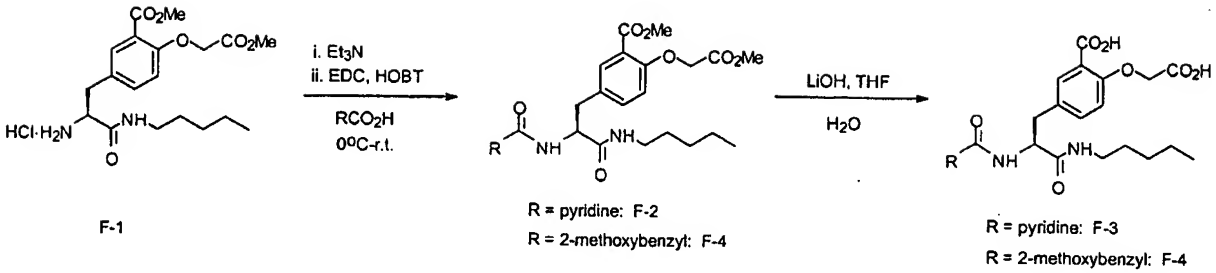

EDC, HOBt
Boc-L-Phe
CH_2Cl_2
Et_3N
$BrCH_2COOMe$
K_2CO_3
acetone
$Sn(Bu)_3$
$Pd_2(dba)_3$
CuI, $AsPh_3$
DMF
6M aq. HCl, THF
Boc_2O, 1M aq. NaOH
dioxane
HCl x
E-1
E-2
E-3
E-4
E-5
E-6

CHART F



F-1

R = pyridine: F-2
R = 2-methoxybenzyl: F-4

R = pyridine: F-3
R = 2-methoxybenzyl: F-4

Table 1

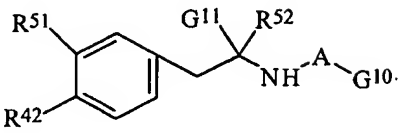
Example Number	Concentration (μM)	% Inhibition	Ki (μM)
13	100 10 1	97 85 43	0.87
12-12	100 10 1	95 76 27	
12-14	100 10 1	94 67 20	
12-16	100 10 1	97 83 38	
12-21	100 10 1	95 73 24	
8	100 10 1		30
1			20
2			46
12-28			0.4
12-2	100 10 1	98 93 64	
12-3	100 10 1	94 72 22	
12-1	100 10 1	97 84 39	
3	100 10 1	80 31 5	
9-2	100 10 1	95 72 23	
9-8	100 10 1	97 81 30	
9-9	100 10 1	97 85 37	
9-11	100 10 1	95 73 22	

9-15	100 10 1	97 31 80	
9-19	100 10 1	98 85 40	
9-20	100 10 1	98 79 27	
9-26	100 10 1	97 78 30	
9-34	100 10 1	96 77 26	
9-1	100 10 1	95 69 18	
11-7	100 10 1	95 69 18	
11-16	100 10 1	95 72 20	

The Ki values were calculated from IC50-values obtained from a dose-response curve prepared using the inhibition assay described above.

CLAIMS

1. Compounds of the formula I:



I

wherein A is –C(O)- or $-SO_2-$;

wherein G^{10} is $-R^{43}$;

wherein G^{11} is

a) $CONR^{99}R^{44}$,

b) H,

c) CH_2OH, or

d) $CH=CHR^{44}$;

wherein R^{99} is H or C_1-C_6 alkyl;

wherein R^{42} is

a) $-OSO_3H$,

b) $-OCH(CO_2R^{46})_2$,

c) $-OCH_2(CO_2R^{46})$,

d) $-OCH(CO_2R^{46})CH_2CO_2R^{46}$,

e) $-OC(CO_2R^{46})=CHCO_2R^{46}$,

f) $-CH_2CH(CO_2R^{46})_2$,

g) $-CH=C(CO_2R^{46})_2$,

h) $-OCH_2CONHOH$,

i) $-N(CH_2CO_2R^{46})_2$, or

j) $-OCHF(CO_2R^{46})$;

wherein R^{43} is

a) -C_1-C_{10} alkoxy,

b) -C_0-C_6 alkyl-$(G^{12})_n$, wherein alkyl is optionally substituted with one to three -O-C_1-C_4 alkyl, halo, or trifluoromethyl, and optionally interrupted with one to three -O-, -S-, or -N-, with the proviso that when G^{12} is phenyl, the phenyl group must be substituted by one (1) to four (4) R^{50} groups, provided that –$COOR^{46}$ is not a substituent,

c) -C_2-C_{10} alkenyl-$(G^{12})_n$,

d) -C_1-C_{10} alkyl-O-$(G^{12})_n$,

e) -C_1-C_6 alkyl-C_3-C_{10} cycloalkyl optionally substituted with one to three R^{50}, or

f) -C_0-C_{10} alkylcarbonyl-$(G^{12})_n$ wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-;

wherein R^{44} is

a) -C_1-C_{12} alkyl, optionally substituted with one to three -O-C_1-C_4 alkyl, -S-C_1-C_4 alkyl, -O-G^{12}, -S-G^{12}, or -OH, and optionally interrupted with one to three -O-, -S-, or -N-,

b) -C_1-C_4 alkyl-C_3-C_6 cycloalkyl,

c) -C_2-C_{12} alkenyl,

d) -C_3-C_{12} alkynyl,

e) -C_0 –C_{10} alkyl$(G^{12})_n$ wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-,

f) -$CH(CONH_2)C_1$-C_{12} alkyl,

g) –C_0-C_6 alkyl-$NR^{53}R^{54}$, wherein alkyl is substituted with zero to three OH,

h) –NR^{54}-CO-R^{56}, or

i) –O-C_1-C_{10} alkyl$(G^{12})_n$, wherein alkyl is optionally interrupted with one to three -O-, -S-, or -N-;

wherein R^{46} is

a) -H,

b) -C_1-C_{10} alkyl, or

c) -C_1-C_5 alkyl-phenyl;

wherein R^{47} is

a) -C_1-C_{10} alkyl,

b) -C_0-C_6 alkyl-G^{12},

c) $-C_1-C_6$ alkyl-$CONH_2$,

d) $-C_1-C_6$ alkyl $NHCO_2R^{46}$,

e) $-C_1-C_6$ alkyl-OR^{46},

f) $-C_1-C_6$ alkyl-$NHSO_2Me$,

g) $-C_1-C_6$ alkyl-O-G^{12},

h) $-C_1-C_6$ alkyl-S-G^{12}, or

i) $-C_1-C_6$ alkyl-CO_2R^{46};

wherein R^{48} is

a) -H,

b) $-C_1-C_6$ alkyl-G^{12},

c) $-C_1-C_6$ alkyl-CO_2R^{46},

d) $-C_1-C_6$ alkyl $CONH_2$,

e) $-C_1-C_6$ alkyl $NHCO_2R^{46}$,

f) $-C_1-C_{10}$ alkyl,

g) $-C_1-C_{10}$ cycloalkyl,

h) $-C_1-C_6$ alkyl-SR^{46}, or

i) $-C_1-C_6$ alkyl-$S(=O)R^{46}$;

wherein G^{12} is

a) phenyl substituted by zero (0) to four (4) R^{50},

b) naphthyl substituted by zero (0) to three (3) R^{50}, or

c) het_1 substituted by zero (0) to three (3) R^{50};

wherein het_1 is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring, C_3-C_8 cycloalkyl, or another heterocycle; and optionally, the nitrogen and sulfur heteroatoms may be in oxidized form;

wherein R^{50} may be any of the following:

a) C_1-C_8 alkyl substituted by zero (0) to three (3) halo,

b) C_2-C_8 alkenyl,

c) OH,

d) O-C_1-C_5 alkyl,

e) O-C_0-C_5 alkyl-phenyl,

f) -$(CH_2)_n$-O-C_1-C_5 alkyl substituted by zero (0) to three (3) hydroxy,

g) -$(CH_2)_n$-O-C_2-C_7 alkenyl substituted by zero (0) to three (3) hydroxy,

h) halo,

i) NH_2,

j) amino-C_1-C_5 alkyl,

k) mono-or di-C_1-C_5 alkylamino,

l) -C(O)-C_1-C_5 alkyl,

m) -CHO,

n) -C(O)-C_0-C_5 alkyl-phenyl,

o) -$COOR^{46}$,

p) -$CON(R^{46})_2$,

q) -C_3-C_7 cycloalkyl,

r) -NO_2,

s) -CN,

t) -SO_3H,

u) -$SO_2N(R^{46})_2$,

v) -$O[(CH_2)_2-O]_n$ -CH_3,

w) -$[CH_2-O]_n$ -C_1-C_3 alkyl,

x) -$NR^{46}(CO)$-NR^{46},

y) -CF_3,

z) - $NR^{46}(CO)C_1$-C_5 alkyl,

a1) -$N(R^{46})$-SO_2-R^{46},

b1) -O-C(O)-R^{46},

c1) -S(O)-R^{46},

d1) -SR^{46},

e1) -SO_2-R^{46},

f1) phenyl, or

g1) oxo;

wherein R^{51} is

a) -H,

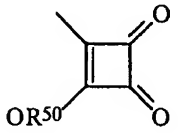
b) -CO_2R^{46},

c) -CONHOH,

d) het_2 substituted by zero to three R^{50}, where in het_2 is a 5- or 6-membered saturated or unsaturated ring containing from one (1) to four (4) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur,

e) F,

f) $OCH_2CO_2R^{46}$, or

g) 

wherein R^{52} is

a) H, or

b) methyl;

wherein R^{53} and R^{54} are

a) H,

b) C_1-C_6 alkyl, or

c) C_0-C_6 alkyl-phenyl;

wherein R^{55} is

a) H, or

b) C_1-C_4 alkyl;

wherein R^{56} is

a) C_0-C_6 alkyl-phenyl, wherein alkyl is optionally substituted with one OH and phenyl is substituted with one to three OH or phenyl, or

b) C_0-C_6 alkyl-NR^{55}-CO-phenyl, wherein alkyl is optionally substituted with one OH and phenyl is substituted with zero to three OH or phenyl;

wherein X is -CO- or $-SO_2-$ or $-CO_2-$;

wherein n is zero, one, two or three;

or a pharmaceutically acceptable salt thereof;

provided that when R^{51} is H, R^{42} is other than $-OCH_2(CO_2R^{46})$; and that when (i) A is $-SO_2-$; and/or (ii) R^{44} is $-C_0$-C_6 alkyl-$NR^{53}R^{54}$, wherein alkyl is substituted with zero to three OH; and/or (iii) R^{44} is $-NR^{54}$-CO-R^{56}; and/or (iv) R^{44} is $-O$-C_1-C_{10} alkyl $(G^{12})_n$, wherein alkyl is

optionally interrupted with one to three -O-, -S-, or -N-; and/or (v) R^{51} is het_2 other than 5-tetrazolyl; and/or (vi) R^{99} is C_1-C_6 alkyl; then

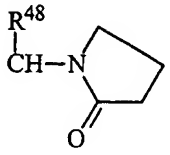
(1) R^{43} may also be

g) -C_1-C_{10} alkyl optionally substituted with (i) one or two -CO_2R^{46} bonded to the same or different carbon atoms or (ii) one –CO-NH_2,

h) –C_0-C_6 alkyl-C_3-C_8 cycloalkyl optionally substituted with one –CO_2R^{46},

i) –C_0-C_6 alkyl-phenyl optionally substituted with (i) one or two –CO_2R^{46} bonded to the same or different carbon atoms or (ii) –$CH_2CH(CO_2R^{46})_2$,

j) –$CH(R^{48})NHXR^{47}$, or

k)  ;

and

(2) G^{10} may also be

b) -$NR^{49}R^{45}$;

wherein R^{45} is

a) -H,

b) -C_1-C_{18} alkyl or alkenyl, or

c) -C_0 –C_6 -alkyl-G^{12}; and

wherein R^{49} is

a) C_0-C_6 alkyl-G^{12},

b) $CH(R^{48})CO_2R^{46}$,

c) $CH(R^{48})CH_2CO_2R^{46}$, or

d) $CH(R^{48})CONHCH_2CO_2R^{46}$.

2. A compound selected from the group consisting of:

2-(carboxymethoxy)-5-[(2S)-3-oxo-3-(pentylamino)-2-({(2S)-2-[(phenoxycarbonyl)amino]-3-phenylpropanoyl}amino)propyl]benzoic acid;

5-((2R)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-{[3-(2-oxo-1-pyrrolidinyl)propyl]amino}propyl)-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-pyridinylmethyl)amino]propyl)-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-isopropoxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(3-hydroxypropyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-[(2R)-2-{[2-(2-methoxyphenyl)acetyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid;

Methyl-2-[4-{(2S)-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetate;

2-[4-{(2S)-2-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5-yl)phenoxy]acetic acid;

2-[4-{(2S)-3-furoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(2H-1,2,3,4-tetrazol-5- yl)phenoxy]acetic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(4-phenylpropoxy)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-[(2-hydroxyethyl)amino]-3-oxopropyl}-2-(carboxymethoxy)benzoic acid;

5-{(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-oxo-3-[(3-phenylpropyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

5-[(2S)-2-({(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}amino)-3-hydroxypropy]-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-2-{[(5,6-dichloro-3-pyridinyl)carbonyl]amino}-3-oxo-3-(pentylamino)propyl]benzoic acid;

5-{(2S)-2-benzoylamino)-3-oxo-3-[(4-phenylbutyl)amino]propyl}-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-{(2S)-2-[(4-chlorobenzoyl)amino]-3-oxo-3-[(4-phenylbutyl)amino]propyl}benzoic acid;

2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(4-phenylbutyl)amino]-2-[(3-pyridinylcarbonyl)amino]propyl}benzoic acid;

2-(carboxymethoxy)-5-{(2S)-2-(3-furoylamino)-3-oxo-3-[(4-

phenylbutyl)amino]propyl}benzoic acid;

5-((2S)-2-(benzoylamino)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)-2-(carboxymethoxy)benzoic acid;

2-(carboxymethoxy)-5-((2S)-2-[(4-chlorobenzoyl)amino]-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-(3-furoylamino)-3-oxopropyl]benzoic acid;

2-(carboxymethoxy)-5-((2S)-2-{[(6-chloro-3-pyridinyl)carbonyl]amino}-3-{[4-(4-methoxyphenyl)butyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-((2S)-3-{[4-(4-chlorophenyl)butyl]amino}-2-{[(2,4-diflurophenyl)sulfonyl]amino}-3-oxopropyl)benzoic acid;

2-(carboxymethoxy)-5-[(2S)-3-{[4-(4-chlorophenyl)butyl]amino}-3-oxo-2-({[(E)-2-phenylethenyl]sulfonyl}amino)propyl]benzoic acid; and

2-(carboxymethoxy)-5-{(2S)-3-oxo-3-[(3-phenoxypropyl)amino]-2-[(phenylsulfonyl)amino]propyl}benzoic acid;

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition, comprising the compounds of claim 1 and a pharmaceutically acceptable carrier.

4. A method for treating a patient by administering an effective amount of a compound of claim 1.

5. A method of inhibiting protein tyrosine phosphatases, comprising contacting a cell with the compounds of claim 1.

6. The method of claim 4, wherein said compound is administered to a human patient.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C237/22 C07K5/06 C07D257/04 C07D405/12 C07D261/12
C07D213/81 C07D237/06 C07D207/26 C07D213/82 C07D307/68
A61K31/165 A61K31/42 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2000	24/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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INTERNATIONAL SEARCH REPORT

Int tional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 96 23813 A (AFFYMAX TECH NV ;PATEL DINESH V (US); GORDEEV MIKHAIL F (US); GORD) 8 August 1996 (1996-08-08) cited in the application the whole document	1-6
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOLE, HEMANTA K. ET AL: "Specific inhibition of insulin receptor dephosphorylation by a synthetic dodecapeptide containing sulfotyrosyl residues as phosphotyrosyl mimetic" retrieved from STN Database accession no. 127:131285 XP002142378 abstract & INDIAN J. BIOCHEM. BIOPHYS. (1997), 34(1&2), 50-55 ,	1-6
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Int. ional Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BURKE, TERRENCE R., JR. ET AL: "Monocarboxylic-based phosphotyrosyl mimetics in the design of Grb2 SH2 domain inhibitors" retrieved from STN Database accession no. 130:332281 XP002142384 abstract & BIOORG. MED. CHEM. LETT. (1999), 9(3), 347-352 ,	1-6
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible compounds. A batch search retrieved over 2000 answers referring to more than 5000 documents. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds wherein R42 represents -OCH2COOR46 and G11 represents -CONR99R44 e.g those compounds prepared in the examples and closely related homologous compounds mentioned in the description in relation with an inhibiting activity of protein tyrosine phosphatase usful for the treatment and/or prevention of diabetes.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/US 00/06022

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